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British Nuclear Medicine Society	Guideline	19	15 - 17	We are concerned that if a service is currently getting good results using Sestamibi as the first line imaging test this can continue (whether an ultrasound is available or not) as the draft guideline shows evidence that the tests have similar results. Sestamibi involves a small dose of radiation and a small increase in costs but the benefits of having successful surgery first time both in terms of morbidity and cost, outweigh these small differences. We note that in the recommendation this relates to – 1.3.2 it says "usually ultrasound" suggesting the committee recognise this. The wording on Pg 19, line 15-17 could be changed to also reflect this.	Thank you for your comment. Based on evidence and experience, the committee agreed that the advantage of ultrasound is that it does not involve any exposure to radiation, and if performed correctly, it can provide very good results. However they considered that ultrasound is very operator dependent and ideally should be performed by a head and neck radiologist. They therefore allowed for sestamibi to be used where the expertise is not available to perform ultrasound. We have edited the rationale section to reflect this.
British Nuclear Medicine Society	Evidence Review D	42	32 - 33	We question why, given the lack of evidence for the pre-operative tests, there has not been a research recommendation made on this?	Thank you for your comment. The committee is able to make a limited set of recommendations for future research and hence considers making those based on the careful consideration of factors including their importance for patients, their potential impact on the NHS and technical feasibility. Other areas where evidence has been lacking such as bone turnover markers and cost-effective management strategies for people whose first surgery for primary hyperparathyroidism has not been successful were considered of greater importance and have hence been prioritised. Please note that in regards to pre-operative imaging, the committee has been able to make consensus based recommendations drawing upon their clinical expertise and are confident these reflect best practice.
Department of Health & Social Care	Guideline	General	General	Thank you for the opportunity to comment on the draft for the above guideline. I wish to confirm that the Department of Health	Thank you for your comment.

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				and Social Care has no substantive comments to make, regarding this consultation.	
Hyperparathyroid UK Action 4 Change	Guideline	General	General	The NHS Constitution refers to and strongly echoes the Absolute Rights of individuals (article 2 - the Right to Life & to be Protected from Neglect) as laid down in the Human Rights Act, and states that the NHS service is *"designed to **improve, prevent, diagnose** and **treat** both physical and mental problems. It is available to all irrespective of gender [and] age. At the same time it has a wider social duty to promote equality through the services it provides and to pay particular attention to groups or sections of society where improvements in health and life expectancy are not keeping pace with the rest of the population".* Likewise, the NICE Charter states that the guidance and quality standards it is supposed to provide are *"based on the **best available evidence** and set out the **best ways to prevent, diagnose and treat disease** and ill-health, promote healthy living and care for vulnerable people".* NICE is *"at the heart of the health and social care system"….[it is] "responsible for providing evidence-based guidance on health and social care"…."to help health, public health and social care professionals deliver the **best possible care** within the resources available".* It is particularly disconcerting, therefore, that almost 65% of the evidence collected in	Thank for your comment. The identified studies were selected for inclusion or exclusion based on criteria that have been agreed with the committee and pre-specified in each evidence review protocol. The protocol, sets out the search criteria and includes information on the optimal study design. In the protocol for evidence report B (see appendix A) the committee agreed the study designs to best answer this question with the lowest level of bias are RCTs (for test-and-treat evidence) and cross-sectional studies / cohort studies / single-gate studies (for diagnostic accuracy evidence). In the committee's expertise and knowledge the evidence published before 2010 was judged to be as clinically relevant as the newer evidence and did not include a data cut off to identify published studies. When making the recommendation the committee discussed the lack of good quality evidence, their experience of current good practice from both a clinical and patient perspective and considered the balance of benefits and costs. The committee recognised the importance of patient experience and this was reflected in the review outcomes, for example quality of life and symptoms. The patient perspective is a key focus of all NICE guidelines and is always taken into consideration during the committee's decision making. This committee had two lay members.

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				Evidence B, to develop the draft guidelines for the diagnosis and initial assessment of disease, pre-dates 1995, with 43% of the evidence being developed in the 1980s. It is also alarming that 11% of the evidence used to create this draft was created in the 1960s and 1970s, which is similar to the amount used (12%) in the 2000s. Only 22% of the evidence used to develop this section of the draft guidance was created since 2010. It appears that only a tiny percentage of the information that was collected was then used in various decision-making processes to inform this section of the draft document. The data used to research and thereby develop the draft guidelines for this section appears to be not only questionable due to its relevance for developing *current* guidelines, but is also extremely limited, dated, selective and ignores a whole body of patient data as well as the significant up-to-date information that is available, if effort had been made to obtain it. Therefore, in order to develop useful, robust guidelines that put patients' lives and health and well-being at the forefront of healthcare, and with reference to the Human Rights Act (*article 2 : the right to life, and the right to be protected from neglect*), it can be argued that decades-old information, that is of questionable value, has no place in the development, distribution and utilisation of guidelines, particularly since it is apparent that these draft guidelines do not fit with many patients' experience of PHPT and is	In order to produce timely NICE clinical guidelines not all topics can be included for consideration by the committee. The topics included were prioritised from the comments received from stakeholders during the scoping consultation. The committee anticipate this guideline will raise general awareness of PHPT and will promote best practice reducing variation in the care people receive.

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				continually contradicted both within the evidence used to develop these draft guidelines, as well as large sources of pertinent information and patient data studies not considered for this body of work by the committee. It is also evident that within the last two years whilst these guidelines were in development, and despite the Hyperparathyroid UK Action 4 Change Group consisting of over 1,390 members either living with the disease or post-surgery, no one from the Committee thought it pertinent to seek information from the very patients whom this disease is currently affecting or has affected. The Human Rights Act (article 2) states that *"public authorities should also consider your right to life when making decisions that might put you in danger or that affect your life expectancy".* Danger (in this case, the unpredictable risk and threat of disease progression in patients with parathyroid disease) and the associated reduction in life expectancy of patients with parathyroid disease does not appear to be at the forefront of the evidence search and subsequent collation. Hence, it could be argued that the subsequent draft guidelines that have been produced have omitted to consider these peoples' rights. It is important to reiterate that these guidelines have indeed been developed using questionable, dated and limited data which has not drawn on a wide range of data that could have been collected if it had been sought. Examples of this given below.	

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				From the Committee's observations stated within the draft guidelines, *"the committee agreed that hyperparathyroid is an under-recognised condition among both the general population and healthcare professionals. They emphasised the importance of accurate, balanced and up-to-date information so that people with the condition can understand it and make informed choices, particularly with regard to surgery"* (Page 26, lines 6-11). Similarly, the vast majority of Action for Change group members have noted the knowledge and expertise of GPs, Endocrinologists and Surgeons unfortunately varies significantly and is sorely lacking in most instances and patients have had to seek information for themselves due to these significant gaps. It is important for these guidelines therefore to include information to raise the awareness of healthcare professionals of such things as how the parathyroid glands work, the whole host of symptoms malfunctioning glands can potentially create and to confirm that calcium levels do not rise as the disease progresses, nor are symptoms fewer for those patients with lower abnormal levels of serum calcium, as many medical professionals currently believe. Healthcare professionals must be made aware of the significant reduction in life expectancy and significantly increased risk to higher incidences of malignancy and cardiovascular disease in untreated parathyroid disease. This would not only allow healthcare professionals	

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				to be better informed to diagnose and treat patients with this disease (and show greater compassion than is sometimes currently shown) but would allow them to be better placed to provide correct information in terms of 'patient information'. Currently, members report a high incidence of incorrect information being given to patients at all points in the system. This is an opportunity to raise awareness, since without this information many healthcare professionals will continue to use guesswork and provide incorrect information as regards this disease. Unfortunately, the committee's emphasis on the importance of *"accurate, balanced, and up-to-date information"* ends there, since much of the evidence gathered is extremely limited, of low value and therefore is not *"based on the* ***best available evidence"*** and consequently has not produced "*the* ***best ways to prevent, diagnose and treat disease*** *and ill-health, promote healthy living and care for vulnerable people".* Nor does it provide up-to-date "*evidence-based guidance on health and social care….to help health, public health and social care professionals deliver the* ***best possible care*** *within the resources available".* It could be argued that much of the low value evidence used, the lack of seeking pertinent information from a wide range of up-to-date sources or information from patients affected by this disease currently (Action for Change members for example) is at odds with the Human Right (article 2) to "*consider your right*	

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				to life when making decisions that might put you in danger or that affect your life expectancy".	
Hyperparathyroid UK Action 4 Change	Guideline	General	General	NICE need to undertake new surveys and questionnaires of patients with a diagnosis of primary hyperparathyroidism including those who have had a successful operation to determine their symptoms, their levels of PTH and calcium and consequent relief of those symptoms after surgery. Our organisation could have significantly contributed to this at any time in the last two years with over 1300 members at various stages of hyperparathyroidism. There is still time before publication of this guideline.	Thank you for your comment. The committee recognised the importance of patient experience and this was reflected in the review outcomes, for example quality of life and symptoms. The patient perspective is a key focus of all NICE guidelines and is always taken into consideration during the committee's decision making. This committee had two lay members. They had broad and extensive knowledge of primary hyperparathyroidism and made a highly valued contribution to the guideline. All members of the committee are equal participants in the process. We have also made recommendations on information and support and on increasing awareness and reducing time to diagnosis.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	The premise of this comment is that the indications for diagnostic testing for primary hyperparathyroidism are scientifically flawed. They are flawed in such a way that any research programmes based on them will be inaccurate and unable to further the aims of the National Health Service in improving health outcomes for the population. The normal range for calcium levels in the general population is based on a study of individuals who are healthy. The results are graphed and displayed as a Bell curve with the outlying results removed at both extremes. The lowest and highest levels of calcium found in this random population of healthy people are taken as the extremes of the range at which any person will be healthy. This interpretation is the first and most important error which must be corrected	Thank you for your comment. Screening calcium was not identified as a topic during the scope consultation. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some normocalcaemia presentations will also be covered by the recommendation on what to do with an albumin-adjusted serum calcium of 2.5 mmol/l or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. For a diagnosis of primary hyperparathyroidism to be made both calcium (on more than one occasion) and PTH need to be considered.

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				before correct diagnosis can be made. The normal range of calcium is taken to be 2.15 – 2.6 at my local laboratory, although this varies from area to area according to local protocols. What this means is that Healthy Person A in the study had a calcium level of 2.15 and Healthy Person Z had a calcium level of 2.6. What it DOES NOT mean is that Heathy Person A will still be healthy if their calcium level rises to 2.6. Nor will Healthy person Z be healthy if their calcium level falls to 2.15. However this is exactly the distortion that the incorrect interpretation of what a normal range means produces. It is taken for medical diagnosis that any patient is healthy if their calcium level is between 2.15 and 2.6. This goes against all the scientific understanding of the endocrine system. Calcium must be maintained within a tight balance for the health of any individual. Healthy Parathyroid glands secrete parathyroid hormone in a pulse in response to a slight drop in calcium availability in order to bring calcium back up to that individual's healthy level. Then pth hormone drops sharply with a half- life of five minutes as soon as calcium is replenished. This is the suppressive relationship. Evidence of this healthy suppressive relationship being disrupted should be used as the diagnostic criteria. If our Healthy Person A with their healthy calcium level of 2.15 has a raise in calcium to say 2.4 due to an adenoma, their calcium level is seriously elevated but still well	The committee noted that the prevalence of primary hyperparathyroidism in those with an albumin-adjusted serum calcium level of 2.6 mmol/litre and over is high. The committee discussed that the prevalence of primary hyperparathyroidism in those with an albumin-adjusted serum calcium of 2.5 mmol/litre and above is lower and therefore testing for PTH is more likely to lead to a greater proportion of unnecessary PTH testing in those who do not have primary hyperparathyroidism and hence incur a high cost. Therefore the committee considered it important that in people with albumin-adjusted serum calcium above 2.5 mmol/litre, only those with a clinical suspicion of primary hyperparathyroidism have a PTH test. Any future updates of this guideline will incorporate new evidence when it becomes available. Screening was not prioritised by the stakeholders during the scoping process The committee addressed individual variation in calcium by recommending repeating the calcium test which is necessary due to random error or changes in the level of physiologically active calcium because of alterations in blood pH or serum albumin. Due to lack of long term, high quality data on individual variation in calcium over the life course, the committee were unable to make any recommendations pertaining to this area.

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				within the normal range. So they won't meet the criteria for a test of parathyroid hormone as they don't officially present with hypercalcaemia. However, if they did get tested the result would show a disrupted suppressive relationship between calcium and pth hormone, i.e. that pth remains elevated consistently over three blood tests and is not supressed by a blood calcium level of 2.4. Take Healthy Person Z with their individual set level of calcium at 2.6. Their calcium level rises due to an adenoma to 2.7 which a much lower rise against their healthy level than person A suffers from, but if they are lucky enough to be tested for calcium they are tagged as hypercalcaemic and may well end up being diagnosed promptly. Person A's disease is more severe and their symptoms may well be more pronounced but they remain undiagnosed and ill and eventually often sadly blamed for their own 'inexplicable' disease. This unfortunately often leads to abuse and misdiagnosis in the mental health system. It also uses up exhaustive amounts of NHS resources economically which must be included in any thorough assessment of the economic impact of an increased testing regime. We have established thus far that each person has their own individual level of calcium in their blood at which they are healthy and health is maintained by homeostasis through a suppressive relationship with parathyroid	

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				hormone. By using the example of two healthy people with individual levels of calcium at different extremes of the population norm we have shown how diagnosis based on hypercalcaemia defined by population range not by individual range can lead to major misdiagnosis and neglect. There are efforts to avoid this within the endocrinology specialism by defining those with calcium in the normal range but who do have adenomas as evidenced by surgery, as a sub set of "Normocalcaemic Hyperparathyroidism' but in reality this is unnecessary if only the reality of individual set calcium levels is recognised and then diagnosis is by evidence of the disruption of homeostasis. This leads on logically to the need for individuals to have their calcium levels recorded at 18 years old while they are healthy in the same way that babies automatically have their blood group recorded. This would show any elevation in later years accurately in the general population who present with generalised malaise with or without renal and bone disease. Any conclusions through research which uses the incorrect diagnostic methods to analyse blood tests for this condition cannot be considered scientifically accurate or appropriate for use in designing a public health response. Current estimates in the US are that 5% of the general population have Primary Hyperparathyroidism. The same should hold for the UK. It is reasonable to state therefore that large numbers of patients are not being	

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				correctly diagnosed and treated. Even ignoring the individual suffering this entails, the economic burden on the NHS must be significant. Given that diagnostic tests are not ordered until the 2.6 level of hypercalcaemia is reached and your documentation reveals time and again that even then studies to date are considered weak and inconclusive, we would suggest that this review needs to recommend relevant research based on correct understanding of the endocrine relationship and its disruption immediately. The present protocols need to be rewritten in their entirety and pathologists and doctors at all levels need to be retrained according to the principles of Endocrinology that are simple once taught correctly, as a matter of urgency. The health crisis in the UK due to unscientific diagnostic methods can then start to be addressed. If the committee members are in any doubt as to the existence of a crisis in regards to this condition, then our group Hyperparathyroid UK Action4change has hundreds of case studies that can be made available for scrutiny with the permission of the individual patient. We would all be extremely grateful to have this contact in order to work together for the relief of this debilitating, life changing and even life threatening condition.	
Hyperparathyroid UK Action 4 Change	Guideline	General	General	There is evidence that Fibromyalgia (FM) symptoms and medication requirements respond to parathyroidectomy (Adkisson et al). FM is characterised by musculoskeletal pain, headaches, depression, fatigue, and cognitive decline, symptoms also seen commonly in	Thank you for your comment. Fibromyalgia was not identified by stakeholders during the scoping process of this guideline but the committee recognised that the symptoms may be similar to primary hyperparathyroidism. We have referred to these symptoms in the committee's discussion of the

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				primary hyperparathyroidism (PHPT). Fibromyalgia patients should be monitored for hyperparathyroidism and the guideline should suggest a diagnosis of Fibromyalgia is not given prior to checking of calcium levels (Costa et al). There should be a link to this guideline from other NICE guidelines such as the "Chronic pain: assessment and management" currently under development. References to follow: Adkisson, C.D., Yip, L., Armstrong, M.J., Stang, M.T., Carty, S.E. and McCoy, K.L., 2014. Fibromyalgia symptoms and medication requirements respond to parathyroidectomy. *Surgery*, *156*(6), pp.1614-1621. Costa, J.M.D.F.T., Ranzolin, A., Costa Neto, C.A.D., Marques, C.D.L. and Duarte, A.L.B.P., 2016. High frequency of asymptomatic hyperparathyroidism in patients with fibromyalgia: random association or misdiagnosis?. Revista brasileira de reumatologia, 56(5), pp.391-397.	evidence in evidence report B. We now cross refer to the Chronic pain guideline in Evidence report A
Hyperparathyroid UK Action 4 Change	Guideline	General	General	The legal 18-week waiting time simply goes out of the window on many occasions regarding this disease due to the incorrect knowledge of medical professionals. These guidelines are an opportunity to educate medical professionals regarding all the potential symptoms, to eliminate the miss-use of serum calcium height being in any way an indicator for surgery and/or number of symptoms any one patient may experience, and to ensure the misery, pain and risk of disease progression is minimised. In addition,	Thank you for your comment. We believe that the recommendation on chronic non-differentiated symptoms will raise awareness of primary hyperparathyroidism. We recommend that a referral for surgery is considered in all people with a diagnosis of PHPT irrespective of calcium level. We anticipate these recommendations will reduce variation in practice and will ensure that people are able to access effective interventions.

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				ensuring that these guidelines (which are almost identical to the horrendously flawed current practice) will stop the misery and distress to patients who have had to fight to get medical help and treatment due to incorrect processes and information being followed for decades.	
Hyperparathyroid UK Action 4 Change	Guideline	General	General	Surgery should be offered regardless of age. Previous thinking suggested that parathyroidectomy should only be offered before age 50. This is clearly outdated now, but is still the case in some hospitals. Please make it clear that there should be no age restriction for surgery, young or old. We all deserve to regain a decent quality of life with a successful parathyroidectomy. www.ncbi.nlm.nih.gov/pubmed/19222492?fbclid=IwAR3VYunft8z-dolUB4ODSKLkUF-G89kh7iKGzDfMSLj5bT1q0VMOSsD5TNg	Thank you for your comment. We have not specified age as an indicator for surgery in this guideline. Age is a protected characteristic under the Equality Act 2010. NICE is fully compliant with this Act and can therefore not discriminate against people due to their age.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	I wish to comment on the stress many of us had to endure fighting for a diagnosis and surgery whilst we progressively deteriorated physically and mentally as we become basically invalids, and how without surgery many of us would have died many years before our time! We had no quality of life! It's that serious! Calcium Is a far greater killer than even high cholesterol.	Thank you for your comment. We anticipate this guideline will raise awareness of PHPT and improve outcomes. The two lay representatives on the committee provided a valuable insight into the challenges of living with primary hyperparathyroidism and we used this to inform the recommendations.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	The use of albumin adjusted serum calcium levels of 2.6 and 2.5 as indicators. This will exclude all patients with normocalcaemic phpt and those whose albumin is at the top of the range which brings the total calcium back within normal range	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the

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					recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	There is no guidance or suggested protocol in the guidelines for the testing of PTH. Numerous studies have shown that PTH degrades extremely quickly and is best tested using EDTA as a preservative. If this is not used the value of the PTH degrades by as much as 20%, particularly where samples are stored for a period of time before testing. Furthermore, the tourniquet should be loosened before the draw of blood for PTH. These should be established as standards within the NHS for the testing of PTH.	Thank you for your comment. As PTH is an unstable element it is important that it is collected safely according to the relevant local laboratory collection protocols. The content of collection protocols are dependent on local circumstances and as such the committee were unable to make useful general recommendations on the content. In the knowledge and experience of the committee using a tourniquet does not make any meaningful difference to calcium. This was not prioritised by the committee as a review question. We have added this detail to the committee's discussion of the evidence in evidence report B. The committee are aware that most laboratories do specify using an EDTA blood collection tube. However specifying the anticoagulant used is not within our scope.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	We are concerned that these guidelines lack up to date relevant research for many sections. Using old medical papers that were undertaken when even less was known and	Thank you for your comment. All of the relevant literature was searched up to 6 August 2018. This is because the committee judged the older evidence to be as clinically relevant as the newer evidence. The

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				fewer diagnosis were made is disappointing when this is the chance to get this right for many patients. These guidelines need to be very clear and specific to primary care in order for them to be confident in treating patients correctly and accurately. It should be challenging old ways of viewing this disease in order to give patients of any age the chance to be cured. Current patients' experiences and symptoms need highlighting. The range of symptoms listed within this document are is not a true reflection. Biochemists often report the inappropriate relationship back to GP/endocrinologists yet this goes unnoticed or the importance of this misunderstood.	committee agreed that a lot of the papers are old but in accordance with the NICE guidelines manual (2014) all applicable research is identified and reviewed. The research recommendations we have made will lead to new research being conducted into key areas of importance. This evidence will be considered when the guideline is updated. Recommendations 1.1.1-1.1.7 are aimed at primary care in recognition of the setting in which the majority of people with PHPT present. The committee have highlighted when calcium and PTH should be measured and the need to seek specialist advice if these indicate a potential PHPT diagnosis. The relationship between symptoms and hypercalcaemia are clear and we have referred to these in the recommendation 1.1.1. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have amended recommendation 1.1.2 to be inclusive of all non-differentiated symptoms associated with PHPT**.** We have removed the examples of symptoms from recommendation 1.1.2 and now list the common symptoms in the section 'terms used in this guideline' and in the committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	It is noticeable that the draft 'initial assessment and diagnosis' and is very similar to the current practice used nationally which many people with elevated calcium levels/parathyroid disease have been fighting against, hence the need for an 'Action 4 Change' group. Currently, it is an unfortunate reality that many	Thank you for your comment. We anticipate the guidelines will improve the diagnosis and management of people with PHPT. The recommendations seek to specify when calcium and PTH should be measured and when to seek advice from a specialist. The committee acknowledged the important role of surgery by recommending that a referral for surgery should be

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				patients with elevated calcium have to fight for treatment/surgical intervention through continual researching, educating the medical professionals in order to fight for their referral to surgery because they don't meet specific criteria, continuous complaining, letter writing, telephone calls and e-mailing, all whilst feeling very ill due to the largely ignored, yet debilitating symptoms of parathyroid disease. Unfortunately, the draft guidelines in terms of the criteria for "Referral for Surgery" are very similar to current practice. It is therefore not possible to see how the degrading and difficult "fight process" that many patients have to endure in order to receive surgical intervention will change.	considered for all people with a diagnosis of PHPT.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	It is worryingly apparent that "the best available evidence" has not been sought or used in the development of these draft guidelines. It is evident that there is an abundance of patient data as well and current information available but has not been gathered or utilised or has simply been ignored. For example, using >2.85mmol/L as one of the criteria for referral for surgery despite there being "no evidence to support this particular cut-off point" (as per Evidence C, 1.9.1.3 'Benefits and Harms') and despite the adjusted serum calcium levels of vast numbers of patients never reaching this level, is particularly concerning. Not only does this go against NICE's own Charter, it most certainly opposes both the NHS Constitution and the Human Rights Act. More specifically, it potentially prevents or	Thank you for your comment. The evidence was searched and identified in accordance with the NICE guidelines manual (2014). All research meeting the criteria specified in the evidence review protocol was systematically reviewed. Details of the protocols can be found in Appendix A of the evidence reports. Albumin-adjusted serum calcium of 2.85 mmol/litre is one of the referral criteria. This level is specified because it is associated with the risks of developing complications. However, we do also recommend that all people with a diagnosis of PHPT should be considered for referral to surgery. We anticipate that these recommendations will ensure that surgery will be offered to all people for whom it is appropriate.

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				delays patients with elevated calcium levels that have not been recorded as >2.85mmol/L from their right to treatment (surgery) and the prevention of progression of the disease, particularly if they also do not have osteopenia/osteoporosis or kidney disease or have a thirst, frequent urination or constipation (the other requirements deemed necessary for surgical intervention according to these draft guidelines). The guidelines vaguely advise that referral to a surgeon should simply be considered if there are other symptoms of primary hyperparathyroidism, without actually spelling out what these symptoms are. This is all nonsense unfortunately. All patients must be considered for surgery, regardless of symptoms or height of abnormal calcium levels, and it is absolutely essential that all potential symptoms are listed to educate medical professionals in this area.	
Hyperparathyroid UK Action 4 Change	Guideline	General	General	The 4th International Workshop on 'Asymptomatic' PHPT published a report in 2014 to assert there is "*a growing consensus that surgery will eventually be appropriate in the vast majority of patients with asymptomatic disease because it is the only definitive therapy".* Indeed, according to Leiffson et al; '*large population-based studies show that patients with PHPT appear to be at risk for premature death. Most of these deaths were due to cardiovascular disease or cancer. This data included both symptomatic and asymptomatic patients; (Current Thinking on Parathyroidism*,	Thank you for your comment. The guideline is permissive about surgery in asymptomatic patients, as there is a recommendation to consider referral for surgery in all people with PHPT irrespective of symptomatology. We have edited the recommendations to emphasise the importance of discussing the benefits and risks of surgery. The committee strongly agree that surgery is the only curative option but that it is not without risks. The statements you refer to in the evidence reports reflect the results of the literature that met the inclusion criteria specified in the review protocol. The committee's discussion of the evidence in the reports reflect their interpretation of the results given their

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				Arrangoiz R, Cordera F et al). This same paper reports "*in a study of **33,346 patients over an 11-year period**, a 20-58% higher mortality [was noted], often of cardiovascular disease in patients with PHPT compared to patients with normal serum calcium levels. Patients who have **early** surgery for parathyroid surgery have improved survival when compared to patients with untreated PHPT. Patients with PHPT have a higher incidence of cardiovascular disease (2.5-3.0 times that of the general population) such as hypertension, left ventricular hypertrophy, heart failure, arrhythmias, stroke and myocardial infarction compared to patients with normal serum calcium levels. Some studies have also shown that the cardiovascular risk returns to normal after a successful surgery, which is important for preventing cardiovascular disease in patients with PHPT. Patients with PHPT have a higher incidence of developing certain malignancies compared to the general population (approximately 2 times higher). The malignancies most commonly associated with PHPT are breast cancer, renal cancer, colorectal cancer, endocrine tumours (adrenals, thymus, pituitary and pancreas), squamous cell carcinoma and prostate cancer"* (Arrangoiz R, Cordera F et al). Similarly, Norman et al also states *"patients with hyperparathyroidism have a higher rate of: stroke, heart failure, heart attack, atrial*	knowledge and experience. In evidence reports C and D we discuss the benefits of surgery. For example, the committee from clinical experience noted that primary hyperparathyroidism patients have lower bone density, increased fracture risk, osteoporosis; and surgery reduces the risk of fracture in such patients. The committee from their clinical experience also discussed that renal stones are one of the end organ effects of primary hyperparathyroidism and the risk of developing renal stones decreases after surgery. The committee recommended that surgery should be considered in people who have risk factors which are predictors of end organ disease or progressive disease. In the reports, the evidence which met the review protocol criteria is presented. Details of the protocols can be found in Appendix A.

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				fibrillation, cardiomyopathy, renal failure, depression, shingles, kidney stones, osteoporosis, serious bone fractures, bone pain, need for hip replacement, GERD, high blood pressure, memory loss, chronic fatigue, MGUS, anaemia...cancers of the breast, colon, kidney and prostate, and early death" (Norman et al Parathyroid.com). In addition, Norman et al also points out that *"all patients with hyperparathyroid disease will develop osteoporosis if the parathyroid tumour is not removed…*[and] *post-menopausal women with parathyroid disease will generally develop osteoporosis 2-5 times faster than their peers".* Thorsen et al conducted a study in Sweden on post-menopausal women with hyperparathyroidism before and one year after parathyroidectomy that *"found a significant increase in bone density in the hip and lower back one year later".* Norman et al confirm that "*parathyroidectomy doesn't just stop the rapid loss of bone density, it allows the body to begin healing itself".* The above information opposes the committee's assertion that *"based on their expertise, the committee agreed that there was no evidence to suggest that surgery modifies cardiovascular disease risk or fracture risk" (Draft guidelines: P25, lines 5-7).* However, if surgery is undertaken early to prevent disease progression and the development of osteoporosis (as well as the various other diseases due to excessive amounts of calcium in the blood), then fracture risk is reduced	

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				since patients either won't have developed osteoporosis or it will prevent the disease from worsening and begin a reversal of the bone loss ie "*it allows the body to begin healing itself".* Similarly, with regards to Evidence C regarding renal function (Page 23, lines 49-51) the draft guideline states *"the committee noted that PHPT is associated with a decline in renal function but there is no evidence that parathyroidectomy leads to an improvement".* On the following page, (Page 24, lines 28-30 of Evidence C), it is noted that the committee makes a remark that opposes their initial assertion, *"the committee, from their clinical experience, also discussed that kidney stones are one of the end organ effects of PHPT and the risk of developing stones decreases after surgery"*. Does this not suggest an improvement? Would this not suggest that a parathyroidectomy, therefore, is key to the **prevention** of a decline in renal function in patients who have not yet developed kidney disease, since the risk of developing stones decreases following surgery? Surely this is evidence that a patient with PHPT who does not have renal function decline should be eligible for surgery and therefore that the criteria laid out in the draft for surgery as regards kidney function/stones is irrelevant? In addition, evidence has been sourced by our Group that states *"after successful parathyroid surgery, bone density improves, fracture*	

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				*incidence is reduced (cohort studies), kidney stones are reduced in frequency among those with a history of renal stones…..[*and] *there may well be improvements in some neurocognitive elements"* (Report: 4th International International Workshop on 'Asymptomatic' PHPT) Again, this is evidence that opposes the committee's assertions. It is also evident that it is needless to single out patients with end organ disease in the criteria for referral. Evidently, the only criteria that needs to be listed is "ALL patients with suspected PHPT, based on blood results must be referred for surgery". Simply include an extra line to state that anyone with end organ disease (including osteoporosis and/or kidney disease) should be marked "urgent". The over-complicated language used in the criteria is just simply confusing and is likely to result in medical professionals only considering those with end organ disease, patients with serum calcium levels of >2.85mmol/L or those with seemingly worsening renal function being referred for surgery and only "consideration" of referral for those patients where disease progression has not yet manifested. This would be wrong and potentially harmful to a vast number of patients, and most certainly at odds with the right to life and the right to be protected from danger laid out in the Human Rights Act. From information such as this it is clear that the best, most up-to-date and accurate information has not been sought to inform	

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				these guidelines. This is extremely worrying to those people with elevated levels of serum calcium/parathyroid disease. It reinforces the fact that ALL patients with hyperparathyroidism should be referred for surgery, without exception or delay. It seems important to reiterate some of the figures within these studies, such as patients with PHPT having a higher incidence (2.5-3 times that of the general population) of cardiovascular disease and a higher incidence of certain malignancies (2 times higher than the general population). Most significant from this information is that p*atients who have **early** surgery for parathyroid surgery have improved survival when compared to patients with untreated PHPT.* These figures are significant and impactful and are unfortunately at odds with the "evidence" utilised by the committee for these guidelines. It is evident from all the above that the draft guidelines and the evidence on which they are based is at best flawed, limited, dated, and far from excellent and at worst, potentially extremely dangerous and life-threatening to patients with parathyroid disease. It could be argued there is an evident lack of substantial, patient-related, informative data to inform these draft guidelines and a gaping chasm of excluded information. This could be considered a breach of Human Rights (article 2) in terms of patients' right to life and their right to life in terms of public authorities not considering evidence that potentially puts them in danger and potentially affect their life expectancy.	

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				Surgical intervention is the ONLY curative option, this should be borne in mind throughout analysis and decision-making processes, regardless of symptoms and height of serum calcium levels. In addition, the Human Rights Act, the NHS Constitution and NICE's own Charter should lay the foundation for seeking accurate, up-to-date, relevant evidence and information, that puts the health and well-being of patients first, rather than an afterthought.	
Hyperparathyroid UK Action 4 Change	Guideline	General	General	Testing for MEN conditions should be discussed more widely and the consultant should make the patient aware of this. Patients should be given the appropriate information to be able to make an informed decision on whether family members should also be tested. Testing centres should be published more widely.	Thank you for your comment. The testing of MEN was outside of the scope of this guideline but we acknowledge that this is an important issue.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	Subsidies/financial help for patients that have to travel well out of their postcode region to be able to access 'specialist' treatment because of it not being available at their local hospital. Treatment of this disease is such a postcode lottery and we have spent thousands of pounds on travelling/hotels/consultations because of not having the expertise on our door step. We travel a 260 mile round trip each time to see the consultant, attend scans and have surgery. Still uncured after 2 surgeries, so this is ongoing for us and has been since 2012.	Thank you for your comment. The committee agreed that this is a very important issue for many people. NICE guidelines are aimed at NHS and social care, subsidies and financial help are not an area that NICE can make recommendations on.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	Please understand and appreciate that our founding member created our organisation	Thank you for your comment. NICE guidelines prioritise evidence from randomised controlled trials,

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				with a goal to achieving production of regulated guidelines for Primary Hyperparathyroidism by the National Institute of Clinical Excellence in the hope this guideline would live up to that title. This guideline as it stands does not live up to our expectation of clinical excellence. We are and always have been very willing to help you achieve this standard, and our comments reflect that idealism. Please do contact us for any assistance by way of evidence and case stories to support our submitted comments.	as these are viewed as the most rigorous design and are least susceptible to bias. The details of the protocols outlining the search criteria for the best available evidence for each review can be found in the protocols in appendix A of the evidence reports. The same principles applied throughout whereby the committee considered that lower quality evidence was more likely to be unreliable and therefore may not assist in making recommendations. The committee considered that performing a systematic review of all lower quality studies would have taken a huge amount of resource and would not have assisted in decision making. making. In areas where no clinical evidence was identified, the committee members used their collective experience to make consensus recommendations. We expect that the guideline will increase awareness of primary hyperparathyroidism including the wide range of symptoms that people may experience. We have sought to make clear recommendations on when advice from a specialist should be sought. All people with the condition should now be considered for referral for surgery. The guideline should reduce variation in practice and improve outcomes for people affected by the condition.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	Primary hyperparathyroidism is a progressive disease which is not mentioned anywhere in this guideline but needs to be brought to the attention of all involved. The longer you have PHPT the more damage it does to your body. Untreated it will eventually ruin the quality of	Thank you for your comment. The committee agreed and we have referred to PHPT as a progressive disease in the committee discussion section of the evidence reviews.

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				one's life and reduce the span of one's life.	
Hyperparathyroid UK Action 4 Change	Guideline	General	General	Nobody knows how bad this disease is until they get it. We believe the amount of people currently diagnosed is the tip of the iceberg. The best thing about this awful, life consuming disease, is that, in the right hands, it is completely curable. We all deserve that chance and increased and regulated awareness will give us all that chance,	Thank you for your comment. We anticipate that these guidelines will raise awareness of the condition and lead to more timely diagnosis
Hyperparathyroid UK Action 4 Change	Guideline	General	General	Busy GP's are not going to have the time to find key facts especially relating to diagnosis that are fragmented and buried in a disjointed manner	Thank you for your comment. The recommendations and algorithms provide clear guidance for people in primary care. An electronic patient pathway will also be available. We anticipate that in combination this will improve primary care management of suspected and diagnosed primary hyperparathyroidism.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	Many of our careers have been put on hold, stopped completely or at the very least affected in some way and absence from work with this disease. We just want surgery so we can get on with our lives.	Thank you for your comment. We anticipate that the guidance will lead to more people being offered referral or being considered for referral for surgery. The recommendations should ensure that surgery is offered to all people for whom it is appropriate, taking into consideration the benefits and risks.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	Patients are often diagnosed when the disease has progressed to the point where they are getting nasty symptoms which indicates they have probably had the disease for years.	Thank you for your comment. We anticipate that the guidance will raise awareness of PHPT and will lead to people being diagnosed sooner.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	All presentations, whether classic PHPT, Normocalcemic PHPT , Normohormonal (Inappropriately supressed PTH) should be managed in the same way whether private or NHS. They are all the same disease, cured by a parathyroidectomy.	Thank you for your comment. This guidance is for NHS settings. We are unable to make recommendations for private practice.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	Given that the NICE Clinical Knowledge Summary for hypercalcaemia; https://cks.nice.org.uk/hypercalcaemia#!topicsummary) itemises confirmation of the diagnosis	Thank you for your comment . In the knowledge and experience of the committee, albumin-adjusted serum calcium measurement could be done with or without a cuff as it would not make any difference in the values

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				of hypercalcaemia requires a blood sample, it states prolonged application of a tourniquet should be avoided. Nowhere in the documents is the use of a tourniquet mentioned let alone discussed. This was raised by us in the consultation on the draft Scope and was supposed to be considered as part of the evidence on diagnostic assessment.	as it is albumin adjusted. This is in the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	Given that the research on measurement of PTH in both serum and EDTA shows a considerable variation in results (up to 25%) the committee do not seem to have considered this aspect nor made recommendations regarding PTH testing. Twomey PJ, Whitlock T, Pledger DR. Journal of Clinical Pathology 2005;58:1000-1001. "intra-individual PTH differences as large as 25.0% can exist on the same day between serum and edentate plasma"	Thank you for your comment. The committee agreed that there is variation but the method of collection was not raised as a topic for a review question by stakeholders in the scoping consultation or by the committee. As PTH is a relatively unstable element it is important that it is collected according to the relevant local laboratory collection protocols. We have added this detail to the committee's discussion of the evidence. The committee are aware that most laboratories do specify using an EDTA blood collection tube. However specifying the anticoagulant is not possible in the absence of a review question on this topic.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	A search of the documents shows the term EDTA only in relation to the discussion on IOPTH. Surely if an IOPTH whilst surgery is ongoing requires the use of EDTA for accurate measurements then a diagnostic test should be to the same standard?	Thank you for your comment. The committee agreed that there is some variation but the method of collection was not raised as a topic for a review question by the committee. As PTH is a relatively unstable element it is important that it is collected according to the relevant local laboratory collection protocols. We have added this detail to the committee's discussion of the evidence in evidence report B.

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					The committee are aware that most laboratories do specify using an EDTA blood collection tube. However specifying the anticoagulant is not possible in the absence of a review question on this topic
Hyperparathyroid UK Action 4 Change	Guideline	General	General	There seem to be many issues upon which the committee has used their clinical experience. Given that the committee's clinical experience is based upon "under-recognised diagnosis in the general population and by health professionals" (to quote the scope document) then surely there is an inherent bias in their clinical experience that would favour prior methods of diagnosis and decision-making and risk repeating the same issues of under-recognised diagnosis?	Thank you for your comment. This guideline was developed in accordance with the NICE guidelines manual (2014). The manual explains how consensus methods can be used where there is no evidence or limited evidence. Whilst primary hyperparathyroidism is under- recognised in general by health professionals the committee was comprised of people with expert knowledge and experience of primary hyperparathyroidism. This included two lay representatives with lived experience of the condition. The committee used their specialist knowledge alongside the identified evidence when making the recommendations. Their discussion of the evidence can be found in all of the evidence reports and is summarised in the rationale and impact section of the short guideline.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	There seem to be many issues upon which the committee has used their clinical experience. Reasoning based on clinical experience, given that "Currently there are no standardised investigations or referral criteria in the UK to guide decision-making in primary care" (scope document)" does not facilitate either an open minded nor a questioning approach to the serious nature of the problem under consideration and seems to fall back on old methodology rather than any evidence based	Thank you for your comment. The guidance was produced in accordance with the NICE guidelines manual (2014). This outlines what to do in the absence of evidence including the guideline committee making consensus recommendations. The committee was comprised of people with knowledge and experience of the primary hyperparathyroidism. This included two lay representatives with lived experience of the condition. The committee used their specialist knowledge alongside the identified evidence when making the recommendations. Their discussion of the

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				reasoning.	evidence can be found in all of the evidence reports and is summarised in the rationale and impact section of the short guideline.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	There seem to be many issues upon which the committee has used their clinical experience. How has the committee's clinical experience been critically appraised for quality and bias? Has this appraisal been undertaken in a manner commensurate with that of other evidence/studies?	Thank you for your comment. The guideline was developed in accordance with the NICE guidelines manual (2014). NICE guidelines prioritise evidence from randomised controlled trials, as these are viewed as of the highest quality for questions on interventions due to their rigorous design that makes them the least susceptible to bias. Where no RCT evidence was available or when RCTs are not the most appropriate study design to answer the question, the committee considered non-randomised evidence/lower quality evidence a priori on a question-by-question basis. The details of this can be found in the protocols in appendix A of the evidence reports. The same principles applied throughout whereby the committee considered that lower quality evidence was more likely to be unreliable and therefore may not assist in making recommendations. The committee considered that performing a systematic review of all lower quality studies would have taken a huge amount of resource and would not have assisted decision making. This guideline has also been the subject of a stakeholder consultation. The committee was comprised of people with knowledge and experience of the primary hyperparathyroidism. recruitment to the committee was aimed at ensuring it was balanced with a spread of clinicians with varying experience and views including lay people. How the committee made the recommendations is captured in the committee's discussion of the evidence in the evidence reports and in the rational and impact sections of the short

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					guideline. Any declarations of interests held by committee members were managed in accordance with the NICE policy in place at the time.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	No evidence is mentioned in the guideline 12 times, Limited evidence 7 times, Lack of evidence 5 times, evidence uncertainty twice and inconsistent evidence once. Who were your researchers? There is an abundance of evidence. We feel opportunities have missed here and feel it is unacceptable.	Thank you for your comment. The guideline was developed in accordance with the NICE guidelines manual (2014). NICE guidelines prioritise evidence from randomised controlled trials, as these are viewed as of the highest quality for questions on interventions due to their rigorous design that makes them the least susceptible to bias. Where no RCT evidence was available or when RCTs are not the most appropriate study design to answer the question, the committee considered non-randomised evidence/ lower quality evidence a priori on a question-by-question basis. The details of this can be found in the protocols in appendix A of the evidence reports. The same principles applied throughout whereby the committee considered that lower quality evidence was more likely to be unreliable and therefore may not assist in making recommendations. The committee considered that performing a systematic review of all lower quality studies would have taken a huge amount of resource and would not have assisted decision making. The committee was comprised of people with knowledge and experience of the primary hyperparathyroidism. How the committee made the recommendations is captured in the committee's discussion of the evidence in the evidence reports and in the rational and impact sections of the short guideline. The committee also identified areas where evidence to answer their review questions was lacking and have used this information to formulate recommendations

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					for future research.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	The collective knowledge and experience of the medical professionals on the Committee with regards to understanding and dealing with hyperparathyroidism and all of its nuances regularly is questionable. Several members do not appear to have any clinical interest in primary hyperparathyroidism based on online research. The members of the Committee who do have endocrinological expertise appear to have other clinical interests which begs the question how much do they really know about hyperparathyroidism? This leaves three out of nine committee members likely with the most knowledge of PHPT, and none of them are women. Considering that the highest number of primary hyperparathyroid patients are reported to be post-menopausal women that is a damning representation. There isn't a single Committee member with a medical background to reflect the other symptoms experienced by patients like a renal specialist, a gynaecologist, a gastroenterologist, a psychiatrist, or a neurologist. There seems to be an unhealthy bias towards those knowledgeable about metabolic bone disorders and very little else yet hyperparathyroidism can give rise to a number of different symptoms and is not limited to metabolic bone disorders.	Thank you for your comment. The guideline committee were recruited on the basis of a number of factors including their expertise in PHPT. The committee represents all of the main specialities that are involved in the diagnosis and management of PHPT. The candidates who best met the pre-specified criteria were recruited.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	There appears to be a lack of formal evidence for symptoms of hyperparathyroidism, our group is an untapped resource for this. We are a self-selecting group as we have sought support and advice for a publically little known	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common

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				and understood disease so may have many interesting case studies available for you to learn from.	symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion in Evidence review A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	I would like to bring to attention issues with correct handling of blood samples for PTH to avoid false low readings. In addition to look at the whole picture, calcium, PTH and Vitamin D need to be taken at the same blood draw. In cases where normocalcemic primary hyperparathyroidism is suspected the use of graphs to plot the relationship is very useful in identifying if the correct suppressive relationship is present.	Thank you for your comment. The committee agreed that there is some variation but the method of collection was not identified as a topic for a review question by the committee. As PTH is a relatively unstable element it is important that it is collected according to the relevant local laboratory collection protocols. We have added this detail to the committee's discussion of the evidence in evidence report B. The committee are aware that most laboratories do specify using an EDTA blood collection tube. However specifying the anticoagulant is not possible in the absence of a review question on this topic.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	There have been numerous people in our organisation who have had or are currently suffering from Normocalcaemic hyperparathyroidism, but this document fails to mention its existence and how it should be treated. That is a gaping void which fails to help patients who are struggling to get a diagnosis.	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic

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					non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B. Any future updates of this guideline will incorporate new evidence when it becomes available.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	By potentially denying the very existence of normocalcaemic hyperparathyroidism as another manifestation of primary hyperparathyroidism, patients with symptoms such as fatigue, bone pain, constipation, osteoporosis/osteopenia, kidney stones, depression will never be tested for hyperparathyroidism if their calcium levels always come out as normal or high normal e.g. 2.45. Yet they may repeatedly have high PTH which goes unchecked for very long periods of time thus worsening the patient's condition. It may well be too late for many who end up with chronic kidney disease or osteoporosis until it becomes apparent that high PTH is the underlying cause. There is far too much emphasis placed on repeat testing for hypercalcaemia when in many cases this will simply not exist but the patient still has hyperparathyroidism.	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B. Any future updates of this guideline will incorporate new evidence when it becomes available.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	The guideline is extremely vague as regards symptoms relating to hyperparathyroidism. There simply is not enough detail on a condition that as it is very few know and	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from

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				actually understand. This guideline does nothing to help raise awareness or educate the medical profession. Whilst I appreciate symptoms can and do vary from one person to the next, there are many symptoms that are common among them that have been given no mention here. E.g. Bone pain, sweating, brain fog and memory issues, anxiety, headaches and migraines, nausea, etc. By only focusing on osteoporosis, renal stones, excessive urination and thirst and constipation, you fail to acknowledge many patients for whom these symptoms either do not present themselves or do not arise at the early stages of hyperparathyroidism. Hyperparathyroidism does not happen overnight. It can take years for a patient to realise they have symptoms because many patients assume some of the symptoms simply relate to ageing. This guideline provides no guidance to both medical professionals and patients on disease progression and what to look out for.	recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion in Evidence review A. We also discuss how testing for albumin-adjusted serum calcium in people with symptoms such as you describe should be made on a case- by-case basis. We expect that recommendation 1.1.2 will raise awareness that people can experience a wide range of symptoms.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	Association with Vitamin D. No effort has been made to clearly differentiate between high PTH arising from low Vitamin D and high PTH arising from primary hyperparathyroidism. Whilst I appreciate the guideline is on primary hyperparathyroidism, failure to clarify how primary hyperparathyroidism differs from secondary hyperparathyroidism and tertiary hyperparathyroidism feels like a missed opportunity to again raise awareness and educate those who have limited experience of dealing with patients that present high PTH.	Thank you for your comment. As you note, this guideline is on primary hyperparathyroidism. Under this guidance clinicians will seek advice from a specialist with expertise in primary hyperparathyroidism for anyone presenting with high PTH (recommendation 1.1.8). We have recommended that vitamin D is checked in secondary care rather than primary care in people with suspected hyperparathyroidism. The committee are confident that in secondary care, the specialists receiving the referrals will understand the distinction

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					between the different forms of hyperparathyroidism.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	Many patients are often told that their high PTH probably relates to low Vitamin D even if their serum adjusted calcium is high. If both calcium and PTH are high, Vitamin D may well be low but it is unlikely to be the underlying cause. Even endocrinologists fail to understand this. Low Vitamin D can give rise to high PTH but does not give rise to high calcium. When both are factors are high, treating patients with Vitamin D on a watch and wait basis is clearly wrong and puts the health of the patient in further jeopardy.	Thank you for your comment. The committee noted that measuring vitamin D and correcting any deficiency is essential in diagnosing and treating people with primary hyperparathyroidism, but noted that correcting a deficiency does not need to precede the diagnosis. The committee discussed that vitamin D can affect the interpretation of the urinary calcium test, hence in people who are vitamin D deficient, the specialist should interpret the urine calcium with caution. Untreated vitamin D deficiency may cause low urine calcium excretion. Correcting any deficiency may reveal normal or even elevated urine calcium excretion. However, the likelihood of a urine calcium result being low is highly unlikely. If this unlikely result is found, it is entirely appropriate to make sure that any vitamin D deficiency has been corrected. If the vitamin D deficiency has been corrected and the urine calcium is low, the diagnosis is the diagnosis is likely to be familial hypocalciuric hypercalcaemia rather than primary hyperparathyroidism. As the likelihood of urine calcium being low even in vitamin deficiency is highly unlikely, the committee did not make this a major feature of the diagnostic algorithm but when urine calcium is low, rarely, there is a major focus on ensuring vitamin D repletion. We have edited the committee's discussion of the evidence in evidence report B to include this detail.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	Whilst reference is made throughout the document on osteoporosis, there is no mention of the pre-cursor i.e. osteopenia. Do patients have to develop osteoporosis before they will be taken seriously by a medical professional? Surely having osteopenia should be an equal if not better indicator of early existence of	Thank you for your comment. DXA is recommended as part of assessment in our recommendations. A referral would be made if low bone density is identified (rather than osteopenia). We consider overarching fracture risk, including bone density, to determine management strategy.

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				hyperparathyroidism. Patients need to be offered surgery well before they reach end organ disease as that is too late for the reversal of certain conditions.	The committee considered using the Z-score as a threshold to define clinically relevant reduction in bone density but recognised that Z-scores are used little in non-specialist clinical practice. The committee recognises that use of T-scores in assessment of calculating overarching fracture risk is far more common place.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	There is absolutely nothing in this draft about raising awareness, providing education and training for endocrinologists about the finer details of primary hyperparathyroidism with all its nuances. For the majority of patients, endocrinologists are their first point of contact after being referred by their GP. Yet based on my experience and the experience of many patients within this group, the majority of endocrinologists seem to be inexperienced, ignorant, incompetent, unhelpful, unaccommodating or any combination of these. It is already difficult for patients who are suffering symptoms that affect the quality of their life to varying degrees to then have to deal with medical professionals who really have no idea or experience with how to deal with these patients. Patients should be able to expect a certain level of care and competence when they are referred to a specialist like an endocrinologist. It is absolutely shocking how little many endocrinologists really know due to insufficient training and experience and yet can be difficult to deal with due to their attitude. Unfortunately, many medical professionals have inflated egos which seem to come before	Thank you for your comment. We have passed your comment on to the NICE implementation team who work with organisations to help to put guidance into practice. We expect this guideline will raise awareness of the condition, improve patient care and reduce variation in practice.

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				the wellbeing of their patients. We cannot allow this to continue.	
Hyperparathyroid UK Action 4 Change	Guideline	General	General	There is a huge emphasis on cost throughout this draft rather than the health and wellbeing of patients. Whilst I understand it is necessary to strike a balance between both, my concern is that by focusing on cost effectiveness alone, recommendations have been proposed that are likely to be cost effective in the short term but will increase the burden on the NHS in the longer term. For example, the emphasis on testing serum calcium alone and offering this repeatedly to patients may be cheap. However, if the patient's health continues to decline because they have primary hyperparathyroidism yet their serum calcium results are not conclusive, to only test serum calcium will never provide the full picture. It is therefore necessary to test PTH and Vitamin D as well as calcium together in order to get a better understanding of a patient's health. Obviously, it will cost more to test all three repeatedly but the likelihood is that it will reduce the time taken to arrive at a diagnosis as compared with only testing serum calcium.	Thank you for your comment. The committee is required to consider both clinical effectiveness and cost effectiveness when making recommendations. The committee need to be increasingly confident in the clinical and cost effectiveness of recommendations if the cost of implementing the recommendation is likely to be substantial (greater than £1million). For many areas in this guideline there was little published clinical and cost effectiveness evidence available to support strong recommendations that would have had significant resource impact, such as undertaking multiple tests for diagnosing PHPT. There was insufficient evidence available to assess the cost effectiveness of undertaking multiple tests for people with PHPT. A particular limitation is the lack of long term published evidence available to demonstrate clinical and cost outcomes in people with a delayed diagnosis compared to those who receive a timely diagnosis. Furthermore, as the prevalence of PHPT is low, the cost effectiveness of such testing is highly uncertain. Therefore, given the potential cost impact of such testing, it could not be recommended.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	Similarly, by declining patients the right to surgery and treating them using non-surgical means increases the burden on the NHS because all symptoms need to be separately managed e.g. prescriptions for Cinacalcet, prescriptions for anti-depressants, prescriptions for pain relief, surgery and hospital stays for recurrent fractures, prescriptions for laxatives, etc. That is a huge ongoing burden on the NHS whereas surgery	Thank you for your comment. Recommendation 1.3.1 and 1.3.2 cover all people with a diagnosis of primary hyperparathyroidism. We have recommended that all people with the condition are either offered a referral for surgery or that such a referral is considered. Surgery might not be suitable or may be declined and we have therefore made recommendations on calcimimetics. The committee recognise that other interventions may be required to manage symptoms.

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				would be much more cost-effective longer term.	
Hyperparathyroid UK Action 4 Change	Guideline	General	General	Having looked at some of the research documents in detail, my general conclusion is that only research that fits the requirements of the guideline seems to have been used. The impression I get is that rather than using current or broad-based research for example on intra-operative PTH monitoring from countries like the US, India, Canada, Australia, etc, what has been used is dated research that supports historic and habitual ways of treating primary hyperparathyroidism so as not to implement a complete change. In that respect I would say the research used is biased as it supports the status quo. What is required is research that supports a complete shift in mind set by the medical profession but unfortunately this is lacking. It is disappointing that an opportunity to really bring about an overhaul in the way primary hyperparathyroidism is managed in the UK by the NHS has been completely overlooked in favour of practises that do not benefit the majority of sufferers.	Thank you for your comment. The guideline was developed in accordance with the NICE guidelines manual (2014). Following NICE processes for guideline development, evidence from randomised controlled trials has been prioritised as these are viewed as of the highest quality for questions on interventions due to their rigorous design that makes them the least susceptible to bias. Where no RCT evidence was available or when RCTs are not the most appropriate study design to answer the question, the committee considered looking at non-randomised evidence/lower quality evidence a priori on a question-by- question basis. Evidence has only been excluded due to its population, interventions, design or variables examined not meeting the criteria specified in our protocols, which are set in advance of searching for the evidence to prevent any bias, and has not been excluded due to the country they have been carried out in or the extent to which it is in line with current practice. When evidence meeting pre-specified standards has not been available, the committee have collectively used their clinical experience to make consensus recommendations. The committee was comprised of people with knowledge and experience of primary hyperparathyroidism. How the committee made the recommendations is captured in the committee's discussion of the evidence in the evidence reports and in the rational and impact sections of the short guideline. We expect that the guideline will increase awareness of primary hyperparathyroidism, including the wide

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					range of symptoms that people may experience. We have sought to make clear recommendations on when advice from a specialist should be sought. All people with the condition should now be considered for referral for surgery. The guideline should reduce variation in practice and improve outcomes for people affected by the condition.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	It is not clear to me how the Committee Membership for developing this draft was arrived at. Whilst I appreciate that a cross-section of professionals is probably necessary. I'm very concerned by the lack of women on the Committee. Julie Cox is the only professional on there and she is a radiologist whose clinical interests are Breast and Intervention Radiology Nuclear Medicine. Does she have any expertise in undertaking radiology on parathyroid patients? Is this a clinical interest of hers? If so then I can find nothing online that demonstrates this. The only other woman on the Committee is Joy Foster who is a lay member. For a condition that affects largely women (but not exclusively) no consideration seems to have been made to have sufficient representation of women on the Committee.	Thank you for your comment. The guideline committee were recruited on the basis of a number of factors including their expertise in PHPT. The committee represents all of the main specialities that are involved in the diagnosis and management of PHPT. The candidates who best met the pre-specified criteria were recruited. Women formed the majority of the evidence in the studies considered by the committee. We have added the issue of gender to the Equality Impact Assessment.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	I'm concerned by the lack of lay members on the Committee i.e. patients who have suffered or continue to suffer with this condition. Two people is simply not enough. Why was there no one from an organisation like Hyperparathyroid UK Action 4 Change not invited to be on the Committee to represent the interests of patients considering it has over	Thank you for your comment. A public consultation was held on the scope and constitution of the guideline committee. The purpose of the consultation is to ensure stakeholder views are captured. No comments were received on the proposal to have two lay representatives on the committee. The two lay representatives were members of different patient organisations. Recruitment to the committee was

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				1000 members? Have patient interests been fully represented in terms of primary hyperparathyroidism, normocalcaemic hyperparathyroidism, normohormonal hyperparathyroidism, those who have needed repeat surgery, those whose condition is being managed with medication, and those who have had minimally invasive surgery vs those who have had 4-gland exploratory surgery? Not possible with only two lay members.	carried out using pre-specified criteria.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	The lack of independence of certain Committee members who have or are likely to have vested interests needs specific mention here. For example, Fausto Palazzo is an eminent endocrine surgeon who I understand performs the maximum number of parathyroid operations in the UK. His stance on normocalcaemic hyperparathyroidism is widely known i.e. he does not recognise it as I have been on the receiving end of this. However, Mr Palazzo has a private practice at the London Endocrine Centre and a look on their website clearly states: *Normocalcaemic Hyperparathyroidism* *Patients with normocalcaemic hyperparathyroidism are normocalcaemic but with a consistently inappropriately elevated PTH in the absence of secondary causes of hyperparathyroidism. The significance of this condition is controversial but once secondary causes of PTH elevation have been excluded there is a suggestion that it may represent the earliest form of pHPT, a phase characterised*	Thank you for your comment. The guideline committee were recruited on the basis of a number of factors including their expertise in PHPT. The committee represents all of the main specialities that are involved in the diagnosis and management of PHPT. The candidates who best met the pre-specified criteria were recruited. Any conflicts of interest were managed in accordance with the NICE policy of declarations of interest in place at the time. The declarations of interests register is published and details the action taken if a member has a conflict of interest We have expanded the discussion of normocalcaemia in the committee's discussion of the evidence in evidence report B.

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				by elevated PTH that leads to a reduced cortical bone density but without hypercalcaemia. The second phase of pHPT is defined by the development of hypercalcaemia and therefore leads to the investigation and diagnosis. *The treatment of normocalcaemic pHPT remains controversial because the emergence of clinical features of pHPT is unpredictable as is the evolution to a hypercalcaemic state. The fact that some patients remain normocalcaemic despite the clinical manifestations of pHPT inevitably raises the question of the definition of a 'normal' serum calcium level for an individual patient. Each patient has to be assessed and treated on their specific merits*.	
Hyperparathyroid UK Action 4 Change	Guideline	General	General	The existence of Normocalcaemic Hyperparathyroidism as just another manifestation of Primary Hyperparathyroidism has not been given any precedence in the draft guideline which of course applies to NHS practices yet we have a surgeon here who will quite happily see patients in his private practice and consider/treat them for normocalcaemic hyperparathyroidism. So, what does this mean? A surgeon who is willing to profit from the misery of patients for his own personal gain. Double standards like this are completely unacceptable. A normocalcaemic patient would have to spend the equivalent of £10,000 (in the absence of medical insurance) to obtain the same treatment that a primary hyperparathyroid patient would be entitled to receive free under the NHS. Patients are being	Thank you for your comment. Any conflicts of interest were managed in accordance with the NICE policy of declarations of interest in place at the time. The declarations of interests register is published and details the action taken if a member has a conflict of interest.

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				discriminated through no fault of their own.	
Hyperparathyroid UK Action 4 Change	Guideline	General	General	The BMJ published a large analysis of 5 clinical trials in 2011. This analysis covers calcium, magnesium and advises that adequate levels of magnesium are essential for the absorption and metabolism of not only calcium but also of vitamin D. Magnesium also draws calcium out of the blood and soft tissues back into the bones, lowering the likelihood of osteoporosis, some forms of arthritis, heart attack and kidney stones! Whilst the relationship between magnesium and vit D is known, it is very disappointing that the importance of that relationship is not evidenced or taken account of in these guidelines.	Thank you for your comment. The committee discussed the role of magnesium but in their knowledge and experience it does do not have a clinically important effect. Magnesium could be an explanation for normocalcaemic PHPT but it is very rare and there is not a straightforward relationship. We recognise the importance of magnesium in calcium homeostasis, but magnesium is usually of relevance with low calcium (i.e. more relevant to hypocalcaemia not hypercalcaemia), but these topics were not prioritised during the scoping process of this guideline.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	Our comments have highlighted the ongoing problem of misdiagnosing people with Normocalcemic Primary Hyperparathyroidism and the huge financial impact that is having on increasing NHS costs as their health deteriorates. We anticipate early diagnosis and treatment will not only give these people back their lives, but will have a positive long term economical saving on wasted NHS funds, waiting times, and consultant appointments, avoiding unnecessary complications and consequent treatments, and with improved awareness and post-operative monitoring, our doctors and endocrinologists will all learn valuable, much needed lessons for the benefits of their patients.	Thank you for your comment. We recognise normocalcaemia and this is covered by recommendation 1.1.4. We recognise that a small number of people have a calcium level below 2.5 mmol/litre but it is not possible to cover all scenarios in a clinical guideline. This guidance do not replace the use of clinical judgement. We have expanded the committee's discussion on this topic in evidence report B.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	We have experience of many patients often told their high PTH probably relates to low Vitamin D even if their serum adjusted calcium	Thank you for your comment. The committee agreed that vitamin D deficiency can lead to a rise in parathyroid hormone (PTH) level, exacerbate bone

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				is high. If both calcium and PTH are high, Vitamin D may well be low but it is unlikely to be the underlying cause. Even endocrinologists fail to understand this. Low Vitamin D can give rise to high PTH but does not give rise to high calcium. When both are factors are high, treating patients with Vitamin D on a watch and wait basis is clearly wrong and puts the health of the patient in further jeopardy.	disease and increase postoperative risk. It is therefore important to assess and correct vitamin D for people with primary hyperparathyroidism. The committee recognises the importance of correcting vitamin D deficiency, but for some primary care providers vitamin D testing is not available. This would slow down referrals from primary care, and can therefore be done in secondary care. The committee agreed that measuring vitamin D and correcting any deficiency is essential in diagnosing and treating people with primary hyperparathyroidism, but noted that correcting a deficiency does not need to precede the diagnosis. This is fully discussed in evidence report B in the committee's discussion of the evidence.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	Whilst reference is made throughout the document on osteoporosis, there is no mention of the pre-cursor i.e. osteopenia. Do patients have to develop osteoporosis before they will be taken seriously by a medical professional? Surely having osteopenia should be an equal to if not a better indicator of early existence of hyperparathyroidism. Patients need to be offered surgery well before they reach end organ disease as that is too late for the reversal of certain conditions. We often see cases of osteopenia being reversed post-surgery.	Thank you for your comment. A referral would be made if low bone density is identified (rather than osteopenia). DXA is recommended as part of assessment in our recommendations.
Hyperparathyroid UK Action 4 Change	Guideline	General	General	Whilst we have mentioned briefly in a couple of comments relating to parathyroid hormone testing, the importance of checking if a patient is on hormone replacement therapy, we feel a more comprehensive comment is required to address the importance of estrogen. Many studies report primary hyperparathyroidism is most common in post-menopausal women. We	Thank you for your comment. We agree it is an important area; however the effect of HRT on PTH levels was not identified as a priority topic during the scoping process.

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				believe the effect of HRT on parathyroid hormone levels is and has been misunderstood for decades meaning some women suffering from menopause, and on estrogen replacement may also be suffering from primary hyperparathyroidism and this is not discovered until estrogen therapy ceases. We would would like to draw your attention to the following studies in order to request an inclusion in this guideline consequently . Although this is an older study from 1993, there follows a study from 2009 and there may even be more recent studies we have not found, but we believe they are an important consideration before ruling out a diagnosis for lower than expected PTH for menopausal women. https://rd.springer.com/article/10.1007%2FBF03348845 *In postmenopausal women PTH suppression by exogenous calcium is reduced. To test whether this finding might be caused by estrogen deficiency 9 postmenopausal women were given transdermal estradiol (E2) treatment for 3 months at a dose of 100 µg/day. PTH reactivity to iv administration of CaCl2 was determined before and at the end of the E2-treatment period. Compliance to treatment was checked by determination of serum levels of E2 and FSH. The E2level rose from 0.1±0.02 (mean±SE) to 0.46±0.10 mmol/l p<0.01), whereas the corresponding FSH level declined from 77.5+7.4 to 33.9±5.7 U/l p<0.01). This suggests good compliance.*	

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				At the end of E2-treatment period calcium administration induced a higher PTH suppression as compared with control value (the PTH decrementai area 2123±270 vs 1253±253 ng/l x min, p<0.05), although a lower calcaemic response was attained (the Ca incremental area 32.6±6.1 vs 47.4±4.5 mmol/l x min, p<0.05). These results imply that parathyroid glands are dependent on an adequate estrogen provision to respond normally to serum calcium changes. *This 2009-2017 study indicates estrogens regulate PTH indirectly:* https://jasn.asnjournals.org/content/jnephrol/20/9/2009.full.pdf The mechanisms by which estrogens modulate PTH are controversial, including whether or not estrogen receptors (ERs) are present in the parathyroid glands. To explore these mechanisms, we combined a rat model of CKD with ovariectomy and exogenous administration of estrogens. We found that estrogen treatment significantly decreased PTH mRNA and serum levels. We did not observe ERα or ERβ mRNA or protein in the parathyroids, suggesting an indirect action of estrogens on PTH regulation. Estrogen treatment significantly decreased serum 1,25(OH)2 vitamin D3 and phosphorus levels. In addition, estrogens significantly increased fibroblast growth factor 23 (FGF23) mRNA and serum levels. In vitro, estrogens led to transcriptional and translational upregulation of FGF23 in osteoblast-like cells in a time- and	

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				concentration-dependent manner. These results suggest that estrogens regulate PTH indirectly, possibly through FGF23. *We have seen studies from the nineties where estrogen therapy was used to treat hyperparathyroidism, so surely this is relevant information to be included in the guideline considering menopausal women*. The following extract is based on this study: **'**Effects of Hormone Replacement Therapy on Bone Mineral Density in Postmenopausal Women With Primary Hyperparathyroidism Four-Year Follow-up and Comparison With Healthy Postmenopausal Women' Brandon J. Orr-Walker, MBChB; Margaret C. Evans, BSc; Judy M. Clearwater; et al 'NEW YORK, July 26 2000 (Praxis Press) Hormone replacement therapy (HRT) is a possible alternative to parathyroidectomy in the treatment of hyperparathyroidism, but the efficacy of HRT in the long-term treatment of chronic stable primary hyperparathyroidism is unclear. To assess this, Orr-Walker and colleagues performed a randomized, placebo-controlled trial of 23 postmenopausal women with primary hyperparathyroidism over the course of 2 to 4 years. Of the 23 women, 11 received HRT and 12 received placebo' A further article discussing PHPT and post-menopausal women; 'Treatments that may improve bone density in HPT include bisphosphonates, estrogen, selective estrogen	

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				receptor modulators, and surgery' https://rd.springer.com/article/10.1385/BMM:3:2:143?fbclid=IwAR2RY1FcAu9sbrDLyP3Ttr6UD6z47iKNi0JC4RzoCZH1pqaaq3vSTQGZ9p4	

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Hyperparathyroid UK Action 4 Change	Guideline	General	General	Whilst we are relieved to see the age restriction of under 50 from your hypercalcemia guideline, has not been added to this guideline, (and should also be removed from your hypercalcemia guideline https://cks.nice.org.uk/hypercalcaemia#!scenario:1), we would very much appreciate a recommendation that age should not be a barrier to surgery because there are some trusts (Scunthorpe being one) who completely refuse to treat people over 50 who have hyperparathyroidism regardless of their calcium level. We have experience of members who are declined treatment who are over 50 and have to get referred out of their area to a surgeon who isn't ageist. We are also aware that the Hammersmith Endocrine Bible for hyperparathyroidism (last updated in 2010) still specifies people under 50 fit the criteria for parathyroid surgery. We have this week seen a communication from one of your committee members stating 'people under 50 years with hyperparathyroidism should be offered surgery irrespective of the level of calcaemia and the same applies to any patient with a corrected calcium greater than 2.85mmol/l irrespective of age. Surgical statics from the BAETS 5th National Audit reveal not all surgeons are not following this protocol, but for some reason we hear it often from doctors and endocrinologists, which obviously prevents a referral. Please include a recommendation against this.	Thank you for your comment. We now discuss that age should not be a barrier to surgery in the Equality Impact Assessment.
Hyperparathyroid UK	Guideline	General	Gener	It has been noted that Committee Membership	Thank you for your comment. The actions taken in

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Action 4 Change			al	consists of 9 out of 14 people for whom there is a direct financial benefit. Out of these 9, only 1 committee member who benefits financially is not allowed to declare or participate in meetings but can answer questions. This must therefore affect the information in the draft guidance document. There are a considerable number of HPT UK Action 4 Change members who have had no alternative but to seek costly, private consultations and treatment for parathyroid disease, predominantly due to the current vast gaps in knowledge of GPs, endocrinologists and surgeons. It is clear that if these draft guidelines to go through without any changes, it would ensure the continued financial benefit for some committee members. For example how much is the average cost of a consultation or surgery for insurance cases and for those who self-pay? This is not indicated in the draft paper but is perhaps key importance in determining key motivations for the content of the draft, much of which is at odds with the views of members of our Action 4 Change organisation, who are clearly not motivated by financial gain, but are the actual people this disease has affected. Committee members should note that these financial benefits are likely to be impacted should the committee decide to consider and make considerable changes to the guidelines as per HPT UK Action 4 Change members' comments. For example; should raising	response to a declared interest by a committee member was in accordance with the NICE policy in place at the time. This policy ensures that any conflicts of interest are managed appropriately and in this case the action taken was to partially exclude the person from the discussion. The interests declared by the rest of the committee were judged not to require any action. Interests termed 'direct financial' are published in the interests of transparency but are rarely specific to the guideline and are therefore not considered conflicts of interest.

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				awareness of this disease be carried out nationally in terms of symptoms, how the parathyroid works, disease progression etc, it is likely people with this disease will be able to satisfactorily obtain treatment on the NHS, rather than being forced to look for private care. It is felt the balance of power on the committee is tipped over-whelming in favour of the committee members who gain financially from this disease. It is felt the committee should be replaced with entirely all members who receive no direct financial gain from this disease in order to ensure that a clear, transparent process is used which reduces the possibility of bias, that disease treatment and prevention are optimised and the possibility of adverse ramifications for patients with parathyroid disease are minimised.	
Hyperparathyroid UK Action 4 Change	Guideline	General	General	We were asked to prioritise our comments as a key stakeholder which is why we obliged by getting them to you before the deadline. This study has been brought to our attention this morning which you may find a useful presentation to the committee. We have raised issues in our comments about people over 50 being refused referrals. https://journals.sagepub.com/doi/10.1177/1179551418815916?icid=int.sj-abstract.similar-articles.2&fbclid=IwAR22pSdwxJogrYD5Q9o0hkcfBe0YqUGP5wTIksTaGCl0R272rMWW41ztTRk#.XDw80cScLsc.facebook	Thank you for your comment. The reference does not meet the protocol criteria for any of the reviews in the guideline. We looked for effectiveness of surgery in all age groups and had included age above 50 years and below 50 years as a subgroup in our surgery review, but we not identify any evidence. Hence in the absence of evidence regarding age and surgical outcomes and in accordance with the NICE equality policy age is not a criteria for surgery. We have shared the reference provided with the committee.

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Hyperparathyroid UK Action 4 Change	Guideline	1	7	This is wrong right from the start. Where is the word curing? *This guideline covers diagnosing, assessing and managing primary hyperparathyroidism. It aims to improve recognition and treatment of this condition, reducing long-term complications and improving quality of life.* It should read: *This guideline covers diagnosing, assessing, managing and curing of primary hyperparathyroidism. It aims to improve recognition and treatment of this condition, reducing long-term complications and improving quality of life*.	Thank you for your comment. The term management has been used to cover all people with PHPT including people who have been cured and those that have not, for example if surgery has been declined or is not appropriate.
Hyperparathyroid UK Action 4 Change	Guideline	3	5	1.1.1 Albumin-adjusted serum calcium is recommended to be used in the diagnosis of PHPT, yet there seems to be contradictions within the document as to which type of calcium is being referred to. We are concerned that these inconsistencies will lead to confusion: Page 14, Line 28: *The committee based their recommendations on the normal reference range for **serum calcium** as defined by the Association of Clinical Biochemistry, which is 2.2 to 2.6 mmol/litre and their own experience. They noted that most people with PHPT have a **serum calcium** above 2.6mmol/litre.* Page 14, Line 6-7**:** *In addition, the committee noted that PHPT is most often discovered after a routine blood test that shows a raised **serum calcium** level.*	Thank you for your comment. We have edited the instances you cite so that they now read albumin-adjusted serum calcium.

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Hyperparathyroid UK Action 4 Change	Guideline	3	5	1.1.1 An accurate calcium status is particularly important in the diagnosis of primary hyperparathyroidism and therefore the most accurate measure available should be utilised, this is not albumin adjusted serum calcium. Whilst ionised calcium is medically proven to be the most accurate measurement, unadjusted calcium is more accurate than albumin adjusted serum calcium in the majority of patients and therefore that should preferred and recommended rather than albumin adjusted serum calcium. With the exception of certain patients, with proven conditions that impact on calcium levels, e.g. those with hypoalbuminemia, non-adjusted calcium is more accurate and therefore should be the test result that is recommended where ionised calcium is not available or considered cost prohibitive. https://bmjopen.bmj.com/content/bmjopen/8/4/e017703.full.pdf	Thank you for your comment. The committee recommended albumin- adjusted serum calcium measurements based on physiology. The committee was confident to recommend this test as adjusted serum calcium has physiological importance. The biological effects of calcium are mediated by free calcium that is not bound to albumin and other proteins. In clinical practice an adjustment is made for serum albumin, which is the most significant protein that calcium binds to. When calcium is bound to this protein, it does not have biological activity. It is the free and metabolically available serum calcium that has biological, physiological and clinical effects. The committee noted that ionised calcium testing cannot be done in primary care and it would usually be undertaken using a blood gas analyser in hospital. They considered that as ionised calcium measurement is a point-of-care test it is not subject to stringent quality control like laboratory-based tests and also the sample has to be handled very quickly, making it a less reliable test.
Hyperparathyroid UK Action 4 Change	Guideline	3	5	1.1.1 Albumin adjusted serum calcium is neither an accurate or reliable measure of calcium status. Although widely adopted as the preferred method for measuring calcium, this goes against evidence that ionised calcium is the most accurate measurement of calcium status as acknowledged by The Associated of Clinical Biochemistry and Laboratory Medicine. http://www.acb.org.uk/docs/default-source/committees/clinical-practice/guidelines/acb-adjusted-calcium-position-paper-march-2015.pdf?sfvrsn=2	Thank you for your comment. The committee recommended albumin- adjusted serum calcium measurements based on physiology. The committee was confident to recommend this test as adjusted serum calcium has physiological importance. The biological effects of calcium are mediated by free calcium that is not bound to albumin and other proteins. In clinical practice an adjustment is made for serum albumin, which is the most significant protein that calcium binds to. When calcium is bound to this protein, it does not have biological activity. It is the free and metabolically available serum calcium that has biological, physiological and clinical effects.

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					The committee noted that ionised calcium testing cannot be done in primary care and it would usually be undertaken using a blood gas analyser in hospital. They considered that as ionised calcium measurement is a point-of-care test it is not subject to stringent quality control like laboratory-based tests and also the sample has to be handled very quickly, making it a less reliable test.
Hyperparathyroid UK Action 4 Change	Guideline	3	5	Albumin adjusted serum calcium should not be recommended in the diagnosis of primary hyperparathyroidism. Medical research and evidence demonstrates that there is not a standardised formula for calculating albumin adjusted serum calcium across all UK labs and this leads to a variation in albumin adjusted calcium results even when patients have the same unadjusted calcium and albumin levels in more than one test. http://www.acb.org.uk/docs/default-source/committees/clinical-practice/guidelines/acb-adjusted-calcium-position-paper-march-2015.pdf?sfvrsn=2. As an example - a patient tested in the same laboratory have had the same non adjusted calcium and albumin levels during tests but each time the corresponding albumin adjusted calcium level reported is different. This is also further exacerbated where patients have one result from one lab (utilised by their primary care setting) and then another test utilising a different lab (utilised in a secondary care setting) with the same non adjusted calcium result but a different adjusted calcium result. This leads to confusion for both patient and	Thank you for your comment. In the absence of published evidence the committee used their knowledge and experience to form this recommendation. The committee was confident to recommend this test as adjusted serum calcium has physiological importance. The biological effects of calcium are mediated by free calcium that is not bound to albumin and other proteins. In clinical practice an adjustment is made for serum albumin, which is the most significant protein that calcium binds to. When calcium is bound to this protein, it does not have biological activity. It is the free and metabolically available serum calcium that has biological, physiological and clinical effects. We recognise that there are different formulae and laboratories have set protocols. It is beyond the remit of this guideline to standardise these.

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				medical professionals involved in their care and leads to prolonged periods of repeated testing which are unnecessary, time consuming and expensive	
Hyperparathyroid UK Action 4 Change	Guideline	3	5	It is vital that calcium is correctly tested, handled in the correct tube, and taken at venepuncture before PTH as EDTA from the PTH vacutainer can cause falsely low calcium readings.	Thank you for your comment. The committee agreed that there is some variation but the method of collection was not identified as a topic for a review question by the committee. As PTH is a relatively unstable element it is important that it is collected according to the relevant local laboratory collection protocols. We have added this detail to the committee's discussion of the evidence in evidence report B. The committee are aware that most laboratories do specify using an EDTA blood collection tube. However specifying the anticoagulant is not possible in the absence of a review question on this topic. We have highlighted this topic with the surveillance review team so that they can search for evidence when it is published. This will be used to inform any update of this guideline.
Hyperparathyroid UK Action 4 Change	Guideline	3	5	By recommending the use of albumin adjusted serum calcium as the measurement used in diagnosing PHPT, patients' true calcium status can be missed, which may lead to an incorrect diagnosis. As an example - patients' with upper normal range serum calcium and normal mid-range albumin produce an adjusted serum calcium level that is considered lower range albumin adjusted calcium. Ionised calcium tested at the same time, reflects the	Thank you for your comment. The committee recommended albumin- adjusted serum calcium measurements based on physiology. The committee was confident to recommend this test as adjusted serum calcium has physiological importance. The biological effects of calcium are mediated by free calcium that is not bound to albumin and other proteins. In clinical practice an adjustment is made for serum albumin, which is the most significant protein that calcium binds to. When calcium is bound to this

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				unadjusted serum calcium, being at the very upper end of the normal range. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3901605/	protein, it does not have biological activity. It is the free and metabolically available serum calcium that has biological, physiological and clinical effects. The committee noted that ionised calcium testing cannot be done in primary care and it would usually be undertaken using a blood gas analyser in hospital. They considered that as ionised calcium measurement is a point-of-care test it is not subject to stringent quality control like laboratory-based tests and also the sample has to be handled very quickly, making it a less reliable test.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	1.1.1 This indicates that only symptoms of hypercalcaemia rather than primary hyperparathyroidism are to be considered, there is medical evidence to support that elevated PTH as well as hypercalcaemia is damaging to various aspects of health.	Thank you for your comment. The committee focused one recommendation on symptoms that are clearly associated with hypercalcaemia. Recommendation 1.1.2 focuses on the symptoms that may be associated with PHPT.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	1.1.1 It is extremely concerning that many of the symptoms experienced by people with high levels of calcium/parathyroid disease are not listed here. The draft document just lists "fatigue or depression" (surely as a minimum, this should be "and/or"). As possible symptoms and in terms of referral for surgery, the criteria only mentions thirst, frequent urination, constipation, end organ disease and the incorrect >2.85mmol/L, pointless stipulation, around serum calcium levels as things to be considered. As an afterthought, a vague point is made *to "consider referral to a surgeon with expertise in parathyroid surgery for people with primary hyperparathyroidism irrespective of the*	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion in Evidence review A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and

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				features listed in recommendation 1.2.1". This excludes the majority of symptoms from which over 95% of patients will potentially be suffering and makes everything far too confusing for medical professionals and patients alike. The only recommendation that needs to be made is that where PHPT is suspected (due to ANY abnormal serum calcium levels on two or more occasions – particularly along with abnormally high parathyroid hormone levels) patients must be referred to an endocrinologist for additional testing prior to surgery.	we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain. The guideline is permissive about surgery in asymptomatic patients, as there is a recommendation to consider referral for surgery in all people with PHPT irrespective of symptomatology. We have edited the recommendations to emphasise the importance of discussing the benefits and risks of surgery. The committee strongly agree that surgery is the only curative option but that it is not without risks.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	1.1.1 Please understand that it feels as though you are trivialising the devastating impact primary hyperparathyroidism has on our lives by ignoring the symptoms so many of us suffer. One of the main reasons we strive so hard for increased awareness is the incredible relief of awful symptoms that a parathyroidectomy brings	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion in Evidence review A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can

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					experience. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	1.1.1 The reality for many people with elevated calcium/parathyroid disease is multiple symptoms that they didn't used to have. Some of these have suddenly appeared, whilst others have been more gradual or noticeably increasing in frequency. Many of these symptoms are inexplicable since there is no other apparent cause of these symptoms. The only common denominator, in general, is elevated calcium and/or elevated parathyroid hormone levels. This is not an either/or situation as indicated by the language chosen in the draft guideline, for many people with abnormally elevated calcium levels there is a long list of multiple symptoms.	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion in Evidence review A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. Some symptoms are most robustly associated with

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				These may not be the symptoms that have been traditionally categorised as symptoms (osteoporosis and kidney disease), and which have been previously, (controversially) considered 'asymptomatic', but they are repeatedly coming up in numerous up-to-date studies and are frequently mentioned by sufferers of abnormally elevated calcium/parathyroid disease (notably those with hypercalcaemia >/= 2.6mmol/L but not necessarily >2.85mmol/L).	hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	1.1.As well as the symptoms of depression and fatigue the draft guideline mentions, symptoms include: insomnia (often chronic), general malaise (feeling unwell/not 100% all the time/frequently), nausea, vomiting, shoulder/neck pain, decreased levels of energy, anxiety and irritability, decreased social interaction, memory loss, decreased concentration, light-headedness, arthralgia, myalgia, bone pain, muscle weakness, intermittent headaches, polydipsia, dry mouth, polyuria, nocturia, anorexia, abdominal pain, heartburn, constipation, diarrhoea/loose stools, palpitations, arrhythmias, elevated blood pressure, hypertension, thinning of the hair (particularly women to the frontal region) and pruritus. There have also been devastating problems with some people with elevated calcium/parathyroid disease having a	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion in Evidence review A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing.

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				decreased ability to complete tasks at home and/or at work (some people/members living with untreated parathyroid disease have had to give up work (me included, despite working full-time the previous 3 decades with rarely a day off) due to the persistent and debilitating symptoms it is deemed unnecessary to include in the draft guideline. These symptoms must all be included in order to raise awareness and to enable medical professionals to question and cross-check with patients the types of symptom they may be experiencing.	Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	1.1.1 No mention of Toxicity Symptoms in this section i.e. Fatigue, Depression, defensiveness and muscle weakness, poor sleep pattern, but added on Page 4 line 3 and referred to as non-specific; I am presuming they are called this as there is no research to link them to the specific symptoms but why wait for 'end organ disease'. As far as I am aware it is known in the medical world that as well as the bones and kidneys, high levels of calcium and PTH effect the muscles, nerves and the gut as well as the emotions as calcium has a sedative effect upon the nervous system and muscular system and which includes both the voluntary and involuntary nervous system, which would indicate that when out of balance the 'non-specific' symptoms appear.	Thank you for your comment. The committee recognised that people may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion in Evidence review A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. The term non-differentiated is used because the symptoms could indicate a number of different conditions and there is not such a robust association with primary hyperparathyroidism. We recognise the impact these symptoms can have on a person's quality of life .
Hyperparathyroid UK	Guideline	3	5-8	1.1.1 A number of our members wanted to	Thank you for your comment. The committee focused

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Action 4 Change				offer comments here because they considered the symptoms listed were simply not indicative of primary hyperparathyroidism. I am concerned that line 7 is in fact incorrect starting with 'symptoms of hypercalcemia'. This is not a guideline for hypercalcemia and should instead read 'Symptoms of Primary Hyperparathyroidism' and be followed with the symptoms listed in the following comments relating to lines 5-8.	one recommendation (1.1.1) on symptoms that are clearly associated with hypercalcaemia. Recommendation (1.1.2) focuses on the symptoms that may be associated with PHPT. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion in Evidence review A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	1.1.1 There are definitely symptoms missing from this list. No mention of bone pain, sleep problems, heart palpitations here.	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion in Evidence review A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	1.1.1 We are concerned that the intended guideline appears to be excluding the increasing numbers of the population diagnosed with normocalcemic primary hyperparathyroidism. We believe it would be a mistake not to amend the guideline accordingly and account for both normocalcemic primary	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the

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				hyperparathyroidism (NCPHPT) and normohormonal primary hyperparathyroidism NHPHPT). We believe not doing so will result in increasing numbers of people remaining undiagnosed and/or certainly untreated and would urge you not to ignore these distinct types of primary hyperparathyroidism. Please read this study presented at the AAES Annual Meeting 2016, entitled: *Differences in single gland and multigland disease are seen in low biochemical profile primary hyperparathyroidism:* https://www.sciencedirect.com/science/article/pii/S0039606016304974 We can provide many case studies of NCPHPT and several case studies of NHPHPT, although there is much evidence already available. Please read this extract from a 2007 study and consider revising lines 7-8 accordingly: 'In *this report, we document our growing experience with normocalcemic PHPT, an experience that has led to new hypotheses about the nature and significance of this clinical finding'* *'Although it was our hypothesis that patients with normocalcemic PHPT represent the earliest clinical manifestation of typical mild asymptomatic PHPT, the data in this report support a more complex picture. Indeed, although many of these patients were initially*	recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded our discussion of normocalcaemic primary hyperparathyroidism in the committee's discussion of the evidence in evidence report B. The committee's definition of PHPT that is used in the guideline does not preclude people with PTH below mid-range being diagnosed with PHPT. Recommendation 1.1.8 – 'Seek advice from a specialist with /expertise in primary hyperparathyroidism if their PTH measurement is…below the midpoint of the reference range with a concurrent albumin-adjusted serum calcium level of 2.6 mmol/litre or above' - includes people with normohormonal PHPT. In this case the GP would perform the PTH test after the second calcium test and given the combination of results would then seek specialist advice. Screening was not prioritised during the scoping process of this guideline. Changes in serum calcium metabolism were not prioritised as a research question by the guideline committee. We have highlighted this topic with the surveillance review team so that any future updates of this guideline will incorporate new evidence when it becomes available.

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				evaluated because of low bone density, there is no evidence of the preponderance of cortical bone loss seen in typical hypercalcaemic patients with mild PHPT. Furthermore, fragility fractures are much more frequent in this cohort than is seen in typical mild PHPT (3). This finding is most likely due to selection bias because more than half of these patients were discovered during evaluation for osteoporosis, fragility fracture, or low BMD. The data in this report suggest that these patients are not the forerunners of mild asymptomatic PHPT. What we and others are describing now is likely to be another presentation of PHPT in which patients have already developed signs and symptoms of the disease but in whom the serum calcium concentrations remain normal. Rather than representing the earliest form of asymptomatic PHPT, the data suggest that these individuals may represent the earliest form of symptomatic PHPT' https://academic.oup.com/jcem/article/92/8/3001/2597709	
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	This list needs to include further symptoms which are medically proven, for example soft tissue calcifications. Three sites of soft tissue calcification occur with hypercalcemia even in the absence of serum phosphate elevations. These are corneal and/or conjunctival calcification, chondrocalcinosis, and renal calcification. Whilst renal stones have been included in the draft, the other two have not been included. Many patients with diagnosed hypercalcaemia and PHPT have corneal/conjunctival calcification and	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion in Evidence review A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can

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				chondrocalcinosis which are treated separately but have not been taken into account during diagnostic work up for PHPT. https://www.ncbi.nlm.nih.gov/books/NBK250/	experience. We expect that recommendation 1.1.2 will raise awareness of the wide range of symptoms that people may experience. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	1.1.1 Other symptoms should be added here. Osteopenia, skeletal pain indicating calcium deposits, early arthritic changes leading to orthopaedic surgeries, frequent headaches, frequent suspected UTIs, depression, anxiety, mood swings, Insomnia. Feelings of 'brain fog', poor memory, confusion, as well as severe and lasting CFS and GERD.	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion in Evidence review A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. We expect that recommendation 1.1.2 will raise awareness of the wide range of symptoms that people

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					may experience. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	1.1.1 Other symptoms should be included. Osteopenia, skeletal pain indicating calcium deposits, early arthritic changes leading to orthopaedic surgeries, frequent headaches, frequent suspected UTIs, depression, anxiety, mood swings, Insomnia. Feelings of 'brain fog', poor memory, confusion.	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion in Evidence review A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. We expect that recommendation 1.1.2 will raise awareness of the wide range of symptoms that people may experience. Some symptoms are most robustly associated with

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					hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	1.1.1 These 3 symptoms are absolutely inadequate with thirst and excessive urination both being symptoms of diabetes I recommend you must add the symptoms listed in your Evidence review here that may otherwise be missed by doctors not reading that far: fatigue, depression, muscle weakness ,constipation, stomach pain, loss of concentration, mild confusion, an incidental abnormal blood test result, neurocognitive	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have amended recommendation 1.1.2 to be inclusive of all non-differentiated symptoms associated with PHPT. We have removed the examples of symptoms from recommendation 1.1.2 and now list the common symptoms in the section 'terms used in this guideline' and in the committee's discussion of the evidence in evidence report A to reflect those mentioned in your comment on the most common symptoms. We expect that recommendation 1.1.2 will raise awareness of the wide range of symptoms that people may experience.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	1.1.1: In my opinion the list of symptoms on lines 7-8 is inadequate and unhelpful to doctors and their patients who may well have had PHPT a considerable length of time before presenting with these symptoms. I feel it would	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common

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				be beneficial to make doctors aware of differential symptoms here rather than 1.1.4 as the following symptoms are more commonly associated with PHPT in our experience as a patient support group of 1390 members. Any combination of bone pain, joint paint, chronic fatigue, headaches, memory loss, confusion, depression, anxiety, thirst, frequent or excessive urination, constipation, osteoporosis/osteopenia, previous fragility fracture or renal stone is more accurate and appropriate here.	symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion in Evidence review A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. We expect that recommendation 1.1.2 will raise awareness of the wide range of symptoms that people may experience.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	1.1.1 Too much emphasis is put on THIRST, increased urination and constipation as symptoms.	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion in Evidence review A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty

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					than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain. We expect that recommendation 1.1.2 will raise awareness of the wide range of symptoms people may experience.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	1.1.1 The word 'a combination' should be included to highlight to medical professionals that any of these symptoms can be an indication of hyperparathyroidism to justify diagnostic testing. From experience, many GPs think a patient needs to present with all symptoms before testing.	Thank you for your comment. The committee agreed and recognised that people may have any of the symptoms we specify and the wording of the recommendation reflects this.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	1.1.1 I do not think the list of symptoms is comprehensive enough. I suggest adding other symptoms such as general feeling of being unwell, deteriorating vision, dry skin patches, sleep disturbances, development of MGUS and abnormal blood protein levels. I can see some of these symptoms have been mentioned later in the document but the first impressions are very important.	Thank you for your comment. Recommendation 1.1.1 focuses on the symptoms most robustly associated with hypercalcaemia. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	Including but not restricted to bone pain, fatigue, thirst, constipation. Use the main symptoms from the questionnaire our members completed as those mentioned here, are in my opinion some of the least impactful.	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have amended recommendation 1.1.2 to be inclusive of all non-differentiated symptoms associated with PHPT. We have removed the examples of symptoms from recommendation 1.1.2 and now list the common symptoms in the section

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					'terms used in this guideline' and the committee's discussion of the evidence in evidence report A. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	Symptoms need to include bone and joint pain, palpitations, anxiety, fatigue, brain fog, especially combined with any of the other symptoms already listed.	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have amended recommendation 1.1.2 to be inclusive of all non-differentiated symptoms associated with PHPT. We have removed the examples of symptoms from recommendation 1.1.2 and now list the common symptoms in the section 'terms used in this guideline' and in the committee's discussion of the evidence in evidence report A. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the

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					symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	Symptoms should also include unexplained fatigue, cognitive dysfunction, bone/joint pain and lethargy. We often see members who have been diagnosed with CFS. There should be a suggestion that GPs/specialists should look at root cause and investigate further.	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have amended recommendation 1.1.2 to be inclusive of all non-differentiated symptoms associated with PHPT. We have removed the examples of symptoms from recommendation 1.1.2 and now list the common symptoms in the section 'terms used in this guideline' and in the committee's discussion of the evidence in evidence report A. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a

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					recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	These symptoms alone could easily be diabetes symptoms which I'm sure many doctors will suspect, so it is worth mentioning here that whilst more symptoms need adding which impact more people such as bone pain, mental disturbances and memory loss; abnormal glucose metabolism and a high prevalence of diabetes have been reported in patients with primary and secondary hyperparathyroidism. Please read these articles and find a place in these guidelines to mention appropriately the effect of Primary hyperparathyroidism on glucose metabolism, corrected post parathyroidectomy. https://www.metabolismjournal.com/article/S0026-0495(00)09635-9/abstract https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2362.1983.tb00116.x?fbclid=IwAR0Muhv3my3qZAOk4XT44UrSUdV_SI28q-fUsgwfTLll-V4aFesySR8dvdc	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have amended recommendation 1.1.2 to be inclusive of all non-differentiated symptoms associated with PHPT. We have removed the examples of symptoms from recommendation 1.1.2 and now list the common symptoms in the section 'terms used in this guideline' and in the committee's discussion of the evidence in evidence report A to reflect those mentioned in your comment on the most common symptoms. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	1.1.1 *Symptoms of hypercalcaemia, such as thirst, frequent or excessive 8 urination, or constipation.* There needs to be more	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of

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				symptoms included. i.e. Bone pain, joint pain.	symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	1.1.1 I believe bone and joint pain should also be added here as they appear to be symptoms experienced by many especially those who have had PHPT more than 5 years.	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and

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					committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	1.1.1 I strongly suggest you increase the symptoms listed here. You state on Page 1 that one of your aims is 'to improve recognition and treatment of this condition, reducing long-term complications and improving quality of life' I don't believe you can achieve this aim without including the following symptoms that blight many peoples' lives with primary hyperparathyroidism, yet are not recognised as symptoms and consequently do not prompt doctors to test for primary hyperparathyroidism: 1. Bone and Joint pain. 2. Anxiety. 3. Depression. 4. Confusion and	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience.

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				memory loss. 5. Sleep disturbances/insomnia. 6. Vision disturbances.	Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	1.1.1 I do not think the list of symptoms is comprehensive enough, I suggest adding other symptoms such as general feeling of being unwell, deteriorating vision, dry patches of skin, and sleep disturbances.	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is

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					not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	1.1.1 Suggested symptoms of hypercalcaemia do not include "effects on the central nervous system such as fatigue and memory impairment" as listed in the final scope document on p 2 of 9. Is there a reason that these symptoms are not listed? I acknowledge that there is recognition of some chronic non-differentiated symptoms on p 4, lines 3-5 however this only suggests *considering* measuring albumin adjusted serum calcium in these cases.	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty

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					than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	1.1.1 The NICE Clinical Knowledge Summary for hypercalcaemia (https://cks.nice.org.uk/hypercalcaemia#!topicsummary) lists a considerable number of clinical features of hypercalcaemia which are not listed here. The guidelines should note that the suggested symptoms are not exhaustive and refer clinicians to the CKS by a hyperlink so that the full extent of clinical features of hypercalcaemia can be considered in deciding whether to measure albumin-adjusted serum calcium.	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is

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					less certain.
Hyperparathyroid UK Action 4 Change	Guideline	3	5-8	R Arrangoiz, F Cordera *et al* in their paper "Current Thinking on Primary Hyperthyroidism" state that "*the vast majority (99.8%) of patients who have an elevated serum calcium level have a problem with one or more of their parathyroid glands. More than 95% of patients with PHPT are symptomatic and only the minority are truly asymptomatic".* Their paper also lists all of the above symptoms. Norman et al (see Parathyroid.com) mentions all of these symptoms and more. There are numerous papers all listing the same or similar findings as regards symptoms. These symptoms, must all be included in this section of the guideline to ensure GPs, Endocrinologists and Surgeons are aware of each patient's possible state of mind as well as their physical state to ensure that not only full consideration of each patient's symptoms are explored but in order for an appropriate level of compassion and understanding to be maintained. It has been reported that patients' concerns are sometimes dismissed or ignored due to the variable knowledge and understanding of the possible impact that elevated calcium levels have on the lives of patients and consequently the levels of distress and sickness with which a patient may be suffering.	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	3	7	1.1.1 A number of our members wanted to offer comments here because they considered the symptoms listed were simply not indicative	Thank you for your comment. In recommendation 1.1.1 we have listed some of the symptoms most robustly associated with

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				of primary hyperparathyroidism. We are concerned that line 7 is in fact incorrect starting with 'symptoms of hypercalcemia'. This is not a guideline for hypercalcemia and should instead read 'Symptoms of Primary Hyperparathyroidism' and be followed with the symptoms listed including the following comments relating to lines 7-8.	hypercalcaemia of primary hyperparathyroidism. We have removed the specific examples from recommendation 1.1.2 and now give a list based on the symptoms provided by you in a comment in the section 'terms used in this guideline'
Hyperparathyroid UK Action 4 Change	Guideline	3	9-10	*1.1.1 osteoporosis or a previous fragility fracture* – to emphasise that this section should be amended to incorporate those with normocalcemic primary hyperparathyroidism (documented as a 3rd era of PHPT in the following 2010 study, by John P.Bilezikian; Shonni J. Silverberg), as well as classic primary hyperparathyroidism, this comprehensive 8 year study of normocalcemic patients indicates: *'Furthermore, fragility fractures are much more frequent in this cohort than is seen in typical mild PHPT'* *http://www.scielo.br/scielo.php?pid=S0004-27302010000200004&script=sci_arttext&tlng=es* *'Primary hyperparathyroidism is a common disorder of mineral metabolism characterized by incompletely regulated, excessive secretion of parathyroid hormone from one or more of the parathyroid glands. The historical view of this disease describes two distinct entities marked by two eras. When primary hyperparathyroidism was first discovered about 80 years ago, it was always symptomatic with kidney stones, bone disease and marked*	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B. We have highlighted this topic with the surveillance review team so that any future updates of this guideline will incorporate new evidence when it becomes available.

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				hypercalcemia. With the advent of the multichannel auto analyzer about 40 years ago, the clinical phenotype changed to a disorder characterized by mild hypercalcemia and the absence of classical other features of the disease. We may now be entering a 3rd era in the history of this disease in which patients are being discovered with normal total and ionized serum calcium concentrations but with parathyroid hormone levels that are consistently elevated'	
Hyperparathyroid UK Action 4 Change	Guideline	3	13-14	1.1.1 The imposition of a minimum level of 2.6 for calcium excludes people with normocalcaemic presentation of phpt and people with high albumin which adjusts the calcium level down. Calcium is kept within a very tight range within the body and any deviation from this range will cause problems. The difficulty is that no one knows what their optimal range is because no testing is carried out until a problem arises. At that point, the best way to obtain a diagnosis is to test calcium and PTH because it is the relationship between the two that is important.	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B. We have highlighted this topic with the surveillance review team so that any future updates of this guideline will incorporate new evidence when it becomes available.
Hyperparathyroid UK	Guideline	3	13-14	I am certain this line: *(2.6 mmol/litre or above),*	Thank you for your comment. The committee stated

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Action 4 Change				should actually read (2.5 mmol/litre or above) to coincide with lines 18/19 which reads: *or 2.5 mmol/litre or above with features of primary hyperparathyroidism.* Otherwise you are contradicting yourself right at the start of the guideline which will only lead to more confusion.	the different level of 2.6 mmol/litre because it is an incidental finding rather than in people presenting to the GP with symptoms.
Hyperparathyroid UK Action 4 Change	Guideline	3	15-16	1.1.2 Ionised calcium is the most accurate measurement of calcium status and if it is considered cost prohibitive to recommend, then the recommendation should be that non adjusted serum calcium should be the test used, which is more accurate and therefore preferable to albumin adjusted serum calcium in all patients except where certain conditions necessitate and adjustment such as hypoalbuminemia. It is unacceptable that the most accurate method of testing is not recommended in diagnosing PHPT.	Thank you for your comment. The committee noted that ionised calcium testing cannot be done in primary care and it would usually be undertaken using a blood gas analyser in hospital. They considered that as ionised calcium measurement is a point-of-care test it is not subject to stringent quality control like laboratory-based tests and also the sample has to be handled very quickly, making it a less reliable test. The committee was confident to recommend adjusted serum calcium as it has physiological importance. The biological effects of calcium are mediated by free calcium that is not bound to albumin and other proteins. In clinical practice an adjustment is made for serum albumin, which is the most significant protein that calcium binds to. When calcium is bound to this protein, it does not have biological activity. It is the free and metabolically available serum calcium that has biological, physiological and clinical effects.
Hyperparathyroid UK Action 4 Change	Guideline	3	15-16	1.1.2 This 2006 study appears to dispute your recommendation. Here is the explanation from that study why ionised calcium should be used wherever possible to guide therapy: https://www.sciencedirect.com/sdfe/pdf/download/eid/3-s2.0-B9780120885626500303/first-page-pdf	Thank you for your comment. The committee noted that ionised calcium testing cannot be done in primary care and it would usually be undertaken using a blood gas analyser in hospital. They considered that as ionised calcium measurement is a point-of-care test it is not subject to stringent

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				'However the corrections for total protein, albumin and pH are in many cases poor substitutes for ionised calcium'	quality control like laboratory-based tests and also the sample has to be handled very quickly, making it a less reliable test.
Hyperparathyroid UK Action 4 Change	Guideline	3	15-16	1.1.2 States explicitly not to measure ionised calcium when testing for primary hyperparathyroidism. There is obviously a cost implication here, but surely it would be cheaper in the long run to measure ionised calcium, at least in patients whose diagnosis is unclear. The opportunity to measure ionised calcium in such cases should not be so dogmatically ruled out in this way, especially as the guidelines are intended for both primary and secondary healthcare professionals. Some members of Hyperparathyroid UK Action4Change were only diagnosed correctly when their ionised calcium levels were found to be high, probably due to inadequacies at the blood draw or laboratory analysis stages. There should be some flexibility here to allow for ionised calcium to be measured if necessary.	Thank you for your comment. The committee noted that ionised calcium testing cannot be done in primary care and it would usually be undertaken using a blood gas analyser in hospital. They considered that as ionised calcium measurement is a point-of-care test it is not subject to stringent quality control like laboratory-based tests and also the sample has to be handled very quickly, making it a less reliable test.
Hyperparathyroid UK Action 4 Change	Guideline	3	15-16	Whether high-range levels of serum calcium, albumin-adjusted calcium or ionised calcium are the deciding factor for a diagnosis of PHPT, the calcium being measured is *calcium which has been drawn into the bloodstream and out of the bones*. Perhaps the committee would consider standardising phlebotomy procedures to include (a) minimum use of a tourniquet, (b) use of **EDTA vials** to retain PTH viability, and (c) setting a maximum time from blood draw to PTH lab analysis due to PTH's very short half-life; and in addition somehow	Thank you for your comment. a) There is no evidence that using or not using a tourniquet makes any meaningful difference to calcium, b) The committee agreed that there is some variation but the method of collection was not identified as a topic for a review question by the committee We have highlighted this topic with the surveillance

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				standardising nationally the methods used to assess albumin-adjusted calcium, plus allowing ionised calcium to be measured in particular cases.	review team so that they can search for evidence when it is published. This will be used to inform any update of this guideline. As PTH is a relatively unstable element it is important that it is collected according to the relevant local laboratory collection protocols. We have added this detail to the committee's discussion of the evidence in evidence report B. The committee are aware that most laboratories do specify using an EDTA blood collection tube. However specifying the anticoagulant is not possible in the absence of a review question on this topic. We have highlighted this topic with the surveillance review team so that they can search for evidence when it is published. This will be used to inform any update of this guideline. c) This is an analytical issue and is dependent upon laboratories locally. All tests should be conducted in quality assured laboratories which will cover all of this. PTH is measured for various diseases not just PHPT so this is a generic point about PTH blood testing and is not about primary hyperparathyroidism only. In the committee's discussion of the evidence in evidence report B we explain that the sample can be cuffed or uncuffed because albumin-adjusted calcium is being measured.
Hyperparathyroid UK Action 4 Change	Guideline	3	15-16	1.1.2: Ionised calcium. I would tend to agree that this would not be the first line of investigation, as it is variable in accuracy and	Thank you for your comment. The committee noted that ionised calcium testing cannot be done in primary care and it would usually be

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				not readily available in all hospitals, other than on blood gas analysers, which are not necessarily adequately calibrated/quality assured for this specific test.	undertaken using a blood gas analyser in hospital. They considered that as ionised calcium measurement is a point-of-care test it is not subject to stringent quality control like laboratory-based tests and also the sample has to be handled very quickly, making it a less reliable test.
Hyperparathyroid UK Action 4 Change	Guideline	3	15-16	1.1.2: Starting with total adjusted calcium is reasonable, but where there is diagnostic uncertainty, particularly where total adjusted calcium is within the upper population reference range (PRR - I tend to prefer this term to 'normal range', as it refers usually to the 95% confidence interval for the test in question, so we accept that 5% of the 'normal' population will have a result outside this range, and that some people with the disease in question will have a result within this range: that is true for practically any diagnostic test, given that none have 100% accuracy). In these circumstances, a high ionised calcium in association with an unsuppressed PTH means that those individuals actually have 'classical' HPT. This is commonly seen in recurrent renal stone disease. I have also seen the occasional patient where total calcium is marginally high, but, due to high levels of binding proteins. Ionised calcium is actually at the lower end of the PRR, hence confirming that those patients did not have HPT after all.	Thank you for your comment. The committee discussed that ionised calcium testing cannot be done in primary care and it would usually be undertaken using a blood gas analyser in hospital. The committee considered that as ionised calcium measurement is a point-of-care test it is not subject to stringent quality control like laboratory-based tests. Furthermore the sample has to be handled very quickly, making it a less reliable test. We have noted this in the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Guideline	3	15-16	Ionised Calcium should be measured as it's a more accurate test and it should be measured especially when the patient has symptoms of hypercalcaemia but their albumin-adjusted serum calcium levels are in the normal range.	Thank you for your comment. The committee noted that ionised calcium testing cannot be done in primary care and it would usually be undertaken using a blood gas analyser in hospital. They considered that as ionised calcium measurement is a point-of-care test it is not subject to stringent

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					quality control like laboratory-based tests and also the sample has to be handled very quickly, making it a less reliable test.
Hyperparathyroid UK Action 4 Change	Guideline	3	15-16	1.1.2 Ionised calcium should be offered to patients when their serum adjusted calcium data does not provide the full picture. To deny patients the right to a diagnostic tool that may well highlight concealed hyperparathyroidism e.g. in patients with normal serum adjusted calcium levels seems poorly thought out. The justification given for not providing this test is insufficiently based on cost alone rather than lack of expertise required to undertake the test.	Thank you for your comment. The committee noted that ionised calcium testing cannot be done in primary care and it would usually be undertaken using a blood gas analyser in hospital. They considered that as ionised calcium measurement is a point-of-care test it is not subject to stringent quality control like laboratory-based tests and also the sample has to be handled very quickly, making it a less reliable test.
Hyperparathyroid UK Action 4 Change	Guideline	3	17-20	We advise the following research should be considered regarding levels of calcium. Research conducted on 20,081 cases is a considerable sample for the committee to consider. Note that this paper refers to serum calcium levels and symptoms: Deva Boone MD et al, 2016: Concentration of serum calcium is not correlated with symptoms or severity of primary hyperparathyroidism: An examination of 20,081 consecutive adults: https://www.sciencedirect.com/science/article/pii/S0039606016305864	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. Based on their clinical experience, the committee recommended performing a PTH test for people with an albumin-adjusted serum calcium level repeatedly 2.6 mmol/litre or above, because they are more likely to have hypercalcaemia, which is a strong indicator of primary hyperthyroidism. For people with an albumin-adjusted serum calcium level repeatedly 2.5 mmol/litre or above and where clinical suspicion of hypercalcaemia is high due to symptoms the committee recommended performing a PTH test. The committee agreed that not all symptoms are specific to primary hyperparathyroidism. There is a small group of patients with primary hyperparathyroidism in whom the calcium may be within the normal range (normocalcaemia) and these patients would fall under the above category. The committee however noted that the vast majority of presentations of primary hyperparathyroidism are in

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					people with hypercalcaemia. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B. We have made the committee aware of the reference.
Hyperparathyroid UK Action 4 Change	Guideline	3	17-20	1.1.3 If this was the cut-off point without also having kidney stones or osteoporosis it completely rules out people with 'normocalcaemic' primary hyperparathyroidism.	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B. Recommendation 1.3.2 states that a referral for surgery should be considered in all people with a diagnosis of primary hyperparathyroidism. We have highlighted this topic with the surveillance review team so that any future updates of this guideline will incorporate new evidence when it becomes available.
Hyperparathyroid UK Action 4 Change	Guideline	3	17-20	1.1.3: I am happy to see '2.5 mmol/litre or above with features of primary hyperparathyroidism' as it is a step in the right	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation

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				direction, but it lacks an explanation of Normocalcemic Primary Hyperparathyroidism which is a distinct form of Primary Hyperparathyroidism, which is detailed in studies as far back as 1992 yet still unrecognised by many doctors. For those of us with lower results, this needs to be compared with corresponding PTH levels always. If we are dependent on elevated calcium levels alone, PHPT would never be detected. Diagnosing primary hyperparathyroidism in any of the 3 recognised distinctions, is about the Ca/PTH relationship, not the independent levels .A select few UK parathyroid surgeons are educated in NCPHPT and successfully cure patients found with one or more adenomas. We are happy to provide you with case stories and clinical evidence upon request.	1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B. We have highlighted this topic with the surveillance review team so that any future updates of this guideline will incorporate new evidence when it becomes available.
Hyperparathyroid UK Action 4 Change	Guideline	3	17-20	1.1.3 Although the full article for this study doesn't advocate surgery it worth noting the conclusion that those with Normocalcemic Primary Hyperparathyroidism had higher risk of high blood pressure than subjects with normal PTH. It is worth considering the necessity of more aggressive therapeutic intervention aimed to normalize PTH even if patients with NPHPT continue to be normocalcemic. https://www.ncbi.nlm.nih.gov/pubmed/25668199?fbclid=IwAR0JcuU12dbk60yeE-DAK2Kq_Wge5qTYWhaYR_626RUCIZwxOMudW3W156Y	Thank you for your comment. Recommendation 1.3.2 states that a referral for surgery should be considered in all people with a diagnosis of primary hyperparathyroidism.
Hyperparathyroid UK	Guideline	3	17-20	1.1.3 Recommendation is to re-test where	Thank you for your comment. The committee

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Action 4 Change				calcium is above 2.6 (or 2.5). With PHPT, adenomas or hyperplasia can often cause erratic and fluctuating results.	discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B. We have highlighted this topic with the surveillance review team so that any future updates of this guideline will incorporate new evidence when it becomes available.
Hyperparathyroid UK Action 4 Change	Guideline	3	17-20	1.1.3 This disjointed sentence; *'If the person's albumin-adjusted serum calcium level is 2.6 mmol/litre or above, or 2.5 mmol/litre or above with features of primary hyperparathyroidism'* reads with more clarity altered to; If the persons' albumin - adjusted calcium level is 2.5 mmol/litre or above with features of primary hyperparathyroidism. It ought to be followed up with a brief explanation of normocalcemic primary hyperparathyroidism such as this: *This guideline recognises normocalcemic primary*	Thank you for your comment. There was recognition that normocalcaemic primary hyperparathyroidism is a relatively recent diagnosis and the natural history of the disease and its optimal management is still unclear. In light of above, the committee therefore agreed that setting a threshold for PTH measurement of albumin-adjusted serum calcium level repeatedly 2.6 mmol/litre or above, or 2.5 mmol/litre or above if there is clinical suspicion of hyperparathyroidism, would identify most people with primary hyperparathyroidism. We have added further information in the rationale and committee's discussion of the evidence in evidence report B.

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				hyperparathyroidism as a specific variation of primary hyperparathyroidism, presenting in people with an albumin-adjusted serum calcium within the normal population range alongside an inappropriately raised parathyroid hormone level. Treatment is the same as for people with classic presentation of primary hyperparathyroidism, a parathyroidectomy is the only cure.	
Hyperparathyroid UK Action 4 Change	Guideline	3 - 4	17 – 20 / 1 - 2	We are concerned that putting both 2.6 and 2.5 calcium levels without including a corresponding PTH may continue to cause confusion within some primary care providers. The importance of a correlating pth level needs to be made very clear.	Thank you for your comment. Recommendation 1.1.6 states that PTH should be measured with a concurrent measurement of the albumin-adjusted serum calcium level.
Hyperparathyroid UK Action 4 Change	Guideline	3 - 4	17 -20 /1 - 2	1.1.3 A short timescale should be added here as currently many endocrinologists suggest every 6 months which adds unnecessary delays to the patient if they are already presenting with symptoms.	Thank you for your comment. No evidence was identified on the timing. The committee discussed adding a time scale but in their knowledge and experience this is dependent on individual circumstances.
Hyperparathyroid UK Action 4 Change	Guideline	3 - 4	17 -20 /1 - 2	1.1.3 Calcium and Parathyroid Hormone (PTH) have to be reviewed in conjunction with each other, as well as Vitamin D rather than stand-alone factors. Looking at calcium and PTH in isolation is a fruitless exercise as both are inter-dependent. When assessing a patient for thyroid disorders, patients are generally tested for Free T3, Free T4 and TSH rather than TSH on its own or Free T3 on its own to arrive at a diagnosis. The same logic should be applied to calcium, PTH and Vitamin D when diagnosing parathyroid disorders.	Thank you for your comment. We do recommend that calcium should be taken at the same time as PTH (recommendation 1.1.6). The committee agreed that measuring vitamin D and correcting any deficiency is essential in diagnosing and treating people with primary hyperparathyroidism, but noted that correcting a deficiency does not need to precede the diagnosis. We recognise the importance of correcting vitamin D deficiency, but for some primary care providers, vitamin D testing is not available. This would slow down referrals from primary care, and can therefore be done in secondary care. The committee discussed that Vitamin D can affect the interpretation of the urinary calcium test, hence in

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					people who are vitamin D deficient, the specialist should interpret the urine calcium with caution. However the likelihood of a urine calcium result being low is highly unlikely and the committee agreed this should not be a major feature of the diagnostic algorithm but when urine calcium is low, rarely, there is a major focus on ensuring vitamin D repletion. We have edited the committee's discussion of the evidence in evidence report B to include this detail. In the experience of the committee the majority of GPs request TSH in isolation.
Hyperparathyroid UK Action 4 Change	Guideline	3 - 4	17 -20 /1 - 2	A standard protocol of testing Calcium/Adjusted calcium, PTH and Vitamin D should be introduced throughout the NHS. The longer-term implications of taking a holistic approach means patients will be diagnosed, treated and cured earlier, resulting in significant reduction of overall cost burden on the NHS, compared to disassociated testing, looking for and testing for other causes of symptoms, repeat GP visits and hospital referrals, repeat hospital visits & stays, GP and hospital prescriptions for managing various symptoms; early diagnosis and surgical cure is overall greatly more cost efficient per patient long term.	Thank you for your comment. Thank you for your comment. The committee discussed the recommendations in relation to your comment and have tried to ensure that they are clear and implementable. We will be passing your thoughts to the implementation team.
Hyperparathyroid UK Action 4 Change	Guideline	3 - 4	17 - 20 /1 - 2	1.1.3 A short timescale should be added here as currently many endocrinologists suggest every 6 months which adds unnecessary delays to the patient if they are already presenting with symptoms.	Thank you for your comment. The committee discussed adding a time frame but in their knowledge and experience this varies according to individual circumstances, for example the calcium level and symptomatology. This is referred to in the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK	Guideline	3 - 4	17 -20	We are concerned the committee considers	Thank you for your comment. The committee

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Action 4 Change			/1 - 2	the level of 2.5mmol/l is more important than looking for an indication the inverse relationship of calcium and parathyroid hormone is malfunctioning in order to believe there could be a chance of PHPT? We have many members who have proven primary hyperparathyroidism when their calcium has not reached that level. Surgeons have operated on people with calcium levels below 2.5 and found adenomas, hyper cellular and hyperplastic glands. It is also well known and proven fact that the blood levels do not indicate a level of how symptomatic a person is.	discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B. We have highlighted this topic with the surveillance review team so that any future updates of this guideline will incorporate new evidence when it becomes available.
Hyperparathyroid UK Action 4 Change	Guideline	3 - 4	17 -20 /1 - 2	1.1.3 Calcium and Parathyroid Hormone (PTH) have to be reviewed in conjunction with each other, as well as Vitamin D rather than stand-alone factors. Looking at calcium and PTH in isolation is a fruitless exercise as both are inter-dependent. When assessing a patient for thyroid disorders, patients are generally tested for Free T3, Free T4 and TSH rather than TSH on its own or Free T3 on its own to arrive at a diagnosis. The same logic should be applied to calcium, PTH and Vitamin D when diagnosing parathyroid disorders.	Thank you for your comment. We do recommend that calcium should be taken at the same time as PTH (recommendation 1.1.6). The committee agreed that measuring vitamin D and correcting any deficiency is essential in diagnosing and treating people with primary hyperparathyroidism, but noted that correcting a deficiency does not need to precede the diagnosis. We recognise the importance of correcting vitamin D deficiency, but for some primary care providers vitamin D testing is not available. This would slow down referrals from primary care, and can therefore be done in secondary care. The committee discussed that Vitamin D can affect the

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					interpretation of the urinary calcium test, hence in people who are vitamin D deficient, the specialist should interpret the urine calcium with caution. However the likelihood of a urine calcium result being low is highly unlikely and the committee agreed this should not be a major feature of the diagnostic algorithm but when urine calcium is low, rarely, there is a major focus on ensuring vitamin D repletion. We have edited the committee's discussion of the evidence in evidence report B to include this detail.
Hyperparathyroid UK Action 4 Change	Guideline	3 - 4	17 – 20 /1 - 2	A standard protocol of testing Calcium/Adjusted calcium, PTH and Vitamin D should be introduced throughout the NHS. The longer-term implications of taking a holistic approach means patients will be diagnosed, treated and cured earlier, resulting in significant reduction of overall cost burden on the NHS, compared to disassociated testing, looking for and testing for other causes of symptoms, repeat GP visits and hospital referrals, repeat hospital visits & stays, GP and hospital prescriptions for managing various symptoms; early diagnosis and surgical cure is overall greatly more cost efficient per patient long term.	Thank you for your comment. We do recommend that calcium should be taken at the same time as PTH (recommendation 1.1.6). The committee agreed that measuring vitamin D and correcting any deficiency is essential in diagnosing and treating people with primary hyperparathyroidism, but noted that correcting a deficiency does not need to precede the diagnosis. We recognise the importance of correcting vitamin D deficiency, but for some primary care providers vitamin D testing is not available. This would slow down referrals from primary care, and can therefore be done in secondary care. The committee discussed that Vitamin D can affect the interpretation of the urinary calcium test, hence in people who are vitamin D deficient, the specialist should interpret the urine calcium with caution. However the likelihood of a urine calcium result being low is highly unlikely and the committee agreed this should not be a major feature of the diagnostic algorithm but when urine calcium is low, rarely, there is a major focus on ensuring vitamin D repletion.

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					We have edited the committee's discussion of the evidence in evidence report B to include this detail.
Hyperparathyroid UK Action 4 Change	Guideline	4	2 - 6	I do not believe that healthcare providers (especially those in primary care – and it is stated that these guidelines are intended for both primary and secondary care) will read far enough through the Rationale pages to see this final recommendation. These lines need to be included at the end of the Context section which begins on page 28, Line 19, to ensure that both primary and secondary healthcare providers are aware that these are guidelines only that may or may not be adhered to at their discretion "***in the light of individual patient circumstances, the wishes of the patient, clinical expertise and resources."***	Thank you for your comment. The additional text would be relevant for a large number of recommendations and reflects standard good clinical practice.
Hyperparathyroid UK Action 4 Change	Guideline	4	3 - 5	1.1.4: Agree, good to recognise that non-specific symptoms merit a serum calcium, amongst other tests.	Thank you for your comment.
Hyperparathyroid UK Action 4 Change	Guideline	4	3 - 5	1.14 R Arrangoiz, F Cordera *et al* in their paper "Current Thinking on Primary Hyperthyroidism" state that "*the vast majority (99.8%) of patients who have an elevated serum calcium level have a problem with one or more of their parathyroid glands. More than 95% of patients with PHPT are symptomatic and only the minority are truly asymptomatic". Symptoms include;* insomnia (often chronic), general malaise (feeling unwell/not 100% all the time/frequently), nausea, vomiting, shoulder/neck pain, decreased levels of energy, anxiety and irritability, decreased social interaction, memory loss, decreased	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have amended recommendation 1.1.2 to be inclusive of all non-differentiated symptoms associated with PHPT. We now list the common symptoms in the section 'terms used in this guideline' and in the committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. Some symptoms are most robustly associated with

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				concentration, light-headedness, arthralgia, myalgia, bone pain, muscle weakness, intermittent headaches, polydipsia, dry mouth, polyuria, nocturia, anorexia, abdominal pain, heartburn, constipation, diarrhoea/loose stools, palpitations, arrhythmias, elevated blood pressure, hypertension, thinning of the hair (particularly women to the frontal region) and pruritus. Norman et al (see Parathyroid.com) mentions all of above symptoms and more. There are numerous papers all listing the same or similar findings as regards symptoms. These symptoms, must all be included in this section of the guideline to ensure GPs, Endocrinologists and Surgeons are aware of each patient's possible state of mind as well as their physical state to ensure that not only full consideration of each patient's symptoms are explored but in order for an appropriate level of compassion and understanding to be maintained. It has been reported that patients' concerns are sometimes dismissed or ignored due to the variable knowledge and understanding of the possible impact that elevated calcium levels have on the lives of patients and consequently the levels of distress and sickness with which a patient may be suffering.	hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	4	3 - 5	It is somewhat reassuring to see fatigue and depression included, although anxiety should also be added, which is also a common presentation in PHPT. To be more specific patients diagnosed with depression/anxiety	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have amended recommendation 1.1.2 to be inclusive of all non-differentiated symptoms

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				which has proven to be treatment resistant to different medications and/or CBT counselling, need to have blood results closely checked (both new and historical). Many have developed these symptoms having never had previous episodes, this and the fact their symptoms are treatment resistant would indicate that it is likely there are other causes of their symptoms, many caused by endocrine disorders, of which PHPT has been proven in many cases to be true. These symptoms have only consequently been resolved after successful diagnosis and surgical cure of PHPT.	associated with PHPT. We have removed the examples of symptoms from recommendation 1.1.2 and now list the common symptoms in the section 'terms used in this guideline' and in the committee's discussion of the evidence in evidence report A .
Hyperparathyroid UK Action 4 Change	Guideline	4	3 - 5	1.1.4 I'm unsure why these symptoms (fatigue and depression) are listed separately from symptoms of thirst, excessive urination and constipation in section 1.1.1. It would make more sense to keep them together as likely symptoms. Anxiety should be included. It is often the first symptom relieved immediately post-surgery. '*consider measuring albumin-adjusted serum calcium'* .should read advise or recommend measuring albumin-adjusted serum calcium as 'consider' suggests fatigue and depression are less important. Atrial fibrillation is another symptom which is not even mentioned here.	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and impact section of the short guideline and in the committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different

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					conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	4	3 - 5	It is important to consider that patients suffering with the cognitive symptoms of PHPT such as fatigue and depression are frequently given a diagnosis of depression/anxiety without proper investigation or consideration of cause. For patients with primary hyperparathyroidism, this diagnosis is often found to be unsatisfactory and inconclusive when looking back through medical history and test results. We see often case stories of people repeatedly told other symptoms, including obvious indications of PHPT such as renal pain/stones, reduced kidney function, osteoporosis are delusional, unrelated and attributable to a mental health condition without appropriate diagnostic tests undertaken. Patients affected by these cognitive symptoms find it very hard to have their voices heard and their physical symptoms addressed. This guideline ought to be mindful of these common occurrences (evidence can be provided) and ensure a recommendation to safeguard this continuing. A recommendation to undertake investigation into physical symptoms presented by these patients would	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a

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				begin to address this.	strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	4	3 - 5	It is important to understand that the cognitive symptoms of PHPT are often ignored and misdiagnosed, leading to inappropriate treatment that is costly to the NHS and detrimental to the patient. These symptoms have a severe impact on quality of life of patient, often leading to loss of income and high levels of economic inactivity and worsening health. Where these symptoms are not alleviated by treatments recommended for depression, testing for PHPT must be considered.	Thank you for your comment. The committee recognised that people may experience a wide range of symptoms including cognition. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience.
Hyperparathyroid UK Action 4 Change	Guideline	4	3 - 5	1.1.4 Our organisation registered as stakeholders on the Depression in Adults guideline because so many (over 90% in a survey) suffered from depression as a symptom of PHPT. Our comments on their draft consultation were dismissed by them as being on the wrong guideline. We would have hoped instead they take our comments seriously, and rule out primary hyperparathyroidism as a cause for depression, posting a link to this guideline. We have experience of a considerable majority of people who suffer from depression as a symptom of primary hyperparathyroidism who are offered unsuccessful therapy of depression without finding the cause. On the basis that 90% of people with hyperparathyroidism suffer from depression which is mostly cured after	Thank you for your comment. The committee wished to emphasise that people may experience many symptoms including depression and these may trigger diagnostic testing. The committee also wanted to make it clear that the common symptoms of hypercalcaemia should lead to diagnostic testing.

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				surgery, we recommend lines 3-5 being removed from here and added to page 3, lines 7-8 (after changing hypercalcemia to primary hyperparathyroidism).	
Hyperparathyroid UK Action 4 Change	Guideline	4	3 - 5	1.1.4 Fibromyalgia needs to be included. Large numbers of patients who are correctly diagnosed with PHPT have already received a diagnosis of fibromyalgia. Many of these patients have historical blood tests that indicate PHPT, but have been ignored for long periods. Both primary care and secondary care diagnosis of fibromyalgia, means no further investigations are carried out for existing or newly presented symptoms that are associated with PHPT. It should not be underestimated how difficult it is for patients to get diagnostic testing for PHPT once they have been given a diagnosis of fibromyalgia, with every symptom being dismissed as part of fibromyalgia and 'untreatable'	Thank you for your comment. We have referred to two of the common symptoms that may be associated with PHPT. Fibromyalgia is one of many possible differential diagnoses and it is not possible to list the symptoms of all of them. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have amended recommendation 1.1.2 to be inclusive of all non-differentiated symptoms associated with PHPT. We now list the common symptoms in the section 'terms used in this guideline' and in the committee's discussion of the evidence in evidence report A to reflect those mentioned in your comment on the most common symptoms.
Hyperparathyroid UK Action 4 Change	Guideline	4	3 - 5	1.1.4 Include fibromyalgia which shares many 'chronic non differentiated symptoms' with PHPT. Considering that fibromyalgia should be a diagnosis of exclusion, large numbers of PHPT patients receive a fibromyalgia diagnosis first, without PHPT being either considered or excluded. Many patients with a diagnosis of fibromyalgia have not had a reoccurrence of fibromyalgia symptoms following successful surgical treatment of PHPT, although it also needs to be recognised that patients with fibromyalgia can also have PHPT too, something frequently disregarded in both primary and secondary care. These conditions are not mutually exclusive.	Thank you for your comment. We have referred to two of the common symptoms that may be associated with PHPT. Fibromyalgia is one of many possible differential diagnoses and it is not possible to list the symptoms of all of them. The guideline committee recognised that people may experience a wide range of symptoms. We have amended recommendation 1.1.2 to be inclusive of all non-differentiated symptoms associated with PHPT. We now list the common symptoms in the section 'terms used in this guideline' and in the committee's discussion of the evidence in evidence report A to reflect those mentioned in your comment on the most

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					common symptoms.
Hyperparathyroid UK Action 4 Change	Guideline	4	3 - 5	1.1.4 The list of symptoms should be expanded to include cognitive dysfunction and bone pain, experienced by many members, even with vitamin D within range. It is often described as one of the worst symptoms experienced by members who have primary hyperparathyroidism for a long period of time, usually greater than five years and is found to be considerably debilitating.	Thank you for your comment. The guideline committee recognised that people may experience a wide range of symptoms. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience.
Hyperparathyroid UK Action 4 Change	Guideline	4	3 - 5	1.1.4 I am concerned that this sentence is unconvincing in relation to clinicians reacting to chronic non-differentiated symptoms and that the words "might" and "consider" would leave many patients untested.	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different

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					conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	4	3 - 5	1.1.4 Please understand that patients are relying on these guidelines to help convince their doctors to request a serum calcium test often after undertaking much research and faced with a doctor who does not believe their symptoms can be caused by primary hyperparathyroidism. I would ask you to list some of the non-specific symptoms you have listed in Evidence Review A, here also, in order to assist the doctor to request the test that you have stated is not an expensive test. It is worthwhile also mentioning that as calcium is regulated by parathyroid hormone, they should be tested together to see a full picture of how they are working in tandem to speed up a diagnosis. As vitamin D can also have an effect on parathyroid and calcium levels, the 3 should be tested together always the first time to save a diagnosis being based on guesswork.	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. In recommendation 1.1.6 we recommend that PTH is measured with a concurrent measurement of albumin-adjusted serum calcium. The committee agreed that measuring vitamin D and correcting any deficiency is essential in diagnosing and treating people with primary hyperparathyroidism, but noted that correcting a deficiency does not need to precede the diagnosis. The committee discussed that for some primary care providers, vitamin D testing is not universally available. They considered that measuring and correcting vitamin D levels before the diagnosis may slow down referrals from primary care, and hence agreed that this test

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					should be performed in secondary care to facilitate a more timely diagnosis. The committee discussed that vitamin D status can affect the interpretation of the urinary calcium test, hence in people who are vitamin D deficient, the specialist should interpret the urine calcium with caution. Untreated vitamin D deficiency may cause low urine calcium excretion. Correcting any deficiency may reveal normal or even elevated urine calcium excretion. However, the likelihood of a urine calcium result being low is highly unlikely. If this unlikely result is found, it is entirely appropriate to make sure that any vitamin D deficiency has been corrected. If the vitamin D deficiency has been corrected and the urine calcium is low, the diagnosis is unlikely to be primary hyperparathyroidism. As the likelihood of urine calcium being low even in vitamin D deficiency is highly unlikely, the committee did not make this a major feature of the diagnostic algorithm but when urine calcium is low, rarely, there is a major focus on ensuring vitamin D repletion. We have edited the committee's discussion of the evidence in evidence report B to include this detail.
Hyperparathyroid UK Action 4 Change	Guideline	4	6 - 8	Please will you address the symptom of chronic fatigue and put links on other guidelines with the symptoms mentioned in this section to avoid years of unnecessary suffering and bring primary hyperparathyroidism to the attention of our general practioners sooner rather than later?	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted

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					serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience.
Hyperparathyroid UK Action 4 Change	Guideline	4	6 - 8	1.1.5 We are extremely concerned that the guideline fails to address the inaccuracy of parathyroid hormone testing in many hospitals and strenuously recommend an inclusion which is beneficial to patients, consultants and will also effect a reduction in wasted tests that are of no benefit to anybody. Please take into account the extensive research we would like to share to emphasise how vital this inclusion is for all concerned: The following extract is taken from this 2002 study: http://clinchem.aaccjnls.org/content/48/5/766 which includes*: iPTH in EDTA is 35% higher in than iPTH in serum at the baseline (all samples tested within 3 hours); After 3 days at room temperature, iPTH in EDTA is roughly similar to its baseline value, whereas iPTH in serum will have decreased by >60% compared to its baseline value.* The Royal Australasian College of Pathologists Quality Assurance Program determines the allowable limits of performance for iPTH assays by two criteria: (a) <25% difference between the sample and the target value when iPTH is >10 pmol/L; and (b) 2.5 pmol/L absolute difference between the sample and target value when the target value is <10 pmol/L. When the Royal Australasian College of Pathologists Quality Assurance Program criteria were applied, 19 of 36 (52%) serum samples at baseline and 27 of 36 (75%) serum samples stored at room temperature for 3 days	Thank you for your comment. As PTH is a relatively unstable element it is important that it needs to be taken according to the relevant laboratory collection protocols. The method of collection was not identified as a topic for a review question by the committee. The committee were aware that most laboratories specify EDTA blood collection tubes. However specifying the anticoagulant is not possible in the absence of a review question on this topic. We have added this detail to the committee's discussion of the evidence in evidence report B.

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				failed assurance criteria, in contrast to one EDTA sample stored at room temperature for 3 days. We defined our reference interval for iPTH (0.8–8.0 pmol/L) according to the values in healthy, vitamin D- sufficient blood donors (7). When we applied this reference interval for iPTH as the diagnostic classification criterion, 6 of 36 (17%) serum samples at baseline and 13 of 26 (50%) serum samples stored at room temperature for 3 days were misclassified, in contrast to two EDTA samples stored at room temperature for 3 days. Despite attempts to analyse serum samples expeditiously, serum values for iPTH were significantly lower than in EDTA-plasma samples. Thus, the IMMULITE 2000 iPTH assay does not give comparable results for serum and EDTA plasma. The further decline in iPTH values in serum at 3 days is consistent with the susceptibility of PTH to degrade in serum samples. As long as adequate sample volume during collection is ensured, EDTA samples are the most appropriate for iPTH measurement by the IMMULITE 2000 immunoassay (6). Use of serum samples for the measurement of iPTH by the IMMULITE 2000 iPTH assay will lead to high rates of diagnostic misclassification unless analysis is carried out promptly and the values are defined by a different reference interval.	
Hyperparathyroid UK Action 4 Change	Guideline	4	6 - 8	1.1.5 This study refers to benefits of frozen samples to both serum and EDTA: PTH in	Thank you for your comment. As PTH is a relatively unstable element it is important that it is taken

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				EDTA, in samples frozen within 30 minutes of collection, is on average 19.5% higher than PTH in serum, in samples frozen within 30 minutes of collection. EDTA samples kept at room temperate saw a decrease in PTH of 14.8% in 48 hours compared to its baseline. PTH in EDTA kept at room temperate after 48 hours is similar to serum PTH frozen within 30 minutes. https://www.ncbi.nlm.nih.gov/pubmed/11587137	according to the relevant laboratory collection protocols. The method of collection was not identified as a topic for a review question by the committee. We have highlighted this topic with the surveillance review team so that they can search for evidence when it is published. This will be used to inform any update of this guideline. The committee were aware that most laboratories specify EDTA blood collection tubes. However specifying the anticoagulant is not possible in the absence of a review question on this topic. We have added this detail the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Guideline	4	6 - 8	1.1.5 The following 2004 study highlights; *At zero time, PTH concentrations in plain serum did not differ (P = 0.431) from those in EDTA plasma. Time delay before freezing had a significant effect on stability in plain serum (P = 0.0106), but not in EDTA plasma (P = 0.642). The PTH concentration decreased significantly after 24 h in plain serum (Table 1). As would be expected, plasma PTH concentrations measured with the second-generation intact PTH assay (median, 193 ng/L; range, 10–709 ng/L) were significantly (P = 0.0098) higher than those measured with the third-generation assay (median, 97 ng/L; range, 34–397 ng/L).* http://clinchem.aaccjnls.org/content/50/9/1713	Thank you for your comment. As PTH is a relatively unstable element it is important that it is taken according to the relevant laboratory collection protocols. The method of collection was not identified as a topic for a review question by the committee. We have highlighted this topic with the surveillance review team so that they can search for evidence when it is published. This will be used to inform any update of this guideline. The committee were aware that most laboratories specify EDTA blood collection tubes. However specifying the anticoagulant is not possible in the absence of a review question on this topic. We have added this detail to the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Guideline	4	6 - 8	*1.1.5 PTH levels in EDTA remain stable up to 12 hours after collection, whereas PTH levels in serum show a reduction of around 10% after*	Thank you for your comment. As PTH is a relatively unstable element it is important that it is taken according to the relevant laboratory collection

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				3 hours. It states that "EDTA tubes are therefore preferable in situations where rapid delivery of blood to the laboratory cannot be achieved." We are concerned that outside testing centres such as DBUH NHS Trust, which has 56 outside testing centres throughout Derbyshire, all testing PTH in serum, are actually producing unreliable results impacting negatively on diagnosis. https://journals.sagepub.com/doi/pdf/10.1258/0004563001899988 Walker, K. and Seth, J. (2000). Stability of parathyroid hormone in blood from renal patients on haemodialysis. *Annals of Clinical Biochemistry*, 37(6), pp.800-801. Which is reinforced by this 2007 study: *The greater stability of PTH in whole blood anticoagulated with potassium EDTA allows PTH analysis to be offered to sites such as satellite clinics and primary care sites which do not have centrifugation and refrigeration facilities*. https://journals.sagepub.com/doi/pdf/10.1258/000456307780480927 English, E., McFarlane, I., Taylor, K. and Halsall, D. (2007). The effect of potassium EDTA on the stability of parathyroid hormone in whole blood. *Annals of Clinical Biochemistry*, 44(3), pp.297-299. Mentions PTH in EDTA is stable for up to at least 20 hours (this is the amount of time they	protocols. The method of collection was not identified as a topic for a review question by the committee. We have highlighted this topic with the surveillance review team so that they can search for evidence when it is published. This will be used to inform any update of this guideline. The committee were aware that most laboratories specify EDTA blood collection tubes. However specifying the anticoagulant is not possible in the absence of a review question on this topic.

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				tested), whereas PTH in serum decreases significantly after 4 hours of collection: PTH in serum, decrease after 8 hours: 10% / after 20 hours: 22%.	
Hyperparathyroid UK Action 4 Change	Guideline	4	6 - 8	1.1.5 The World Health Organisation study from 2002: *Page 39 of this document states the WHO recommends testing PTH (parathyrin = parathyroid hormone) recommends testing PTH in EDTA. It also mentions it can be tested in serum but the remarks state "15% lower concentrations in serum compared to EDTA plasma."* http://apps.who.int/iris/bitstream/handle/10665/65957/WHO_DIL_LAB_99.1_REV.2.pdf;jsessionid=C32647AE3F2CDE562E2D668DDCAAE767?sequence=1	Thank you for your comment. As PTH is a relatively unstable element it is important that it is taken according to the relevant laboratory collection protocols. The method of collection was not identified as a topic for a review question by the committee. We have highlighted this topic with the surveillance review team so that they can search for evidence when it is published. This will be used to inform any update of this guideline. The committee were aware that most laboratories specify EDTA blood collection tubes. However specifying the anticoagulant is not possible in the absence of a review question on this topic. We have added this detail to the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Guideline	4	6 - 8	1.1.5 This study from 2013 quite clearly states reasons for accuracy when testing PTH, considering those with CKD. We have members with CKD whose hospitals are testing PTH in serum: *Parathyroid hormone (PTH) is an 84 amino acid peptide hormone which has important physiological roles in regulating bone metabolism. It stimulates renal reabsorption of calcium, bone resorption and activation of vitamin D, while also inhibiting renal phosphate reabsorption, bone formation and bone mineralisation. PTH measurement is integral to the diagnosis and*	Thank you for your comment. As PTH is a relatively unstable element it is important that it is collected according to the relevant laboratory collection protocols. The method of collection was not identified as a topic for a review question by the committee. The committee were aware that most laboratories specify EDTA blood collection tubes. However specifying the anticoagulant is not possible in the absence of a review question on this topic. We have added this detail to the committee's discussion of the evidence.

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				management of hypoparathyroidism and hyperparathyroidism. Patients with chronic kidney disease (CKD), which is associated with progressive loss of renal mass and consequent reduction in the activation of vitamin D [1], may develop chronic kidney disease-mineral bone disorder (CKD-MBD). Current guidelines recommend that PTH should be maintained within two to nine times the upper limit of the reference interval in CKD-MBD patients [2]. The researchers from this journal fully reviewed and included 83 journal articles. They concluded; *at room temperature, PTH was stable in EDTA preserved whole blood for at least 24 hours; in EDTA plasma for at least 48 hours after collection. PTH was lower in clotted blood samples after 3 hours and in serum after 2 hours. At 4°C PTH was stable in EDTA plasma for at least 72 hours vs. serum (at least 24 hours).* The authors concluded the following: With respect to analytic stability ex vivo, most studies, with both second and third generation assays, indicate PTH to be more stable in EDTA whole blood than clotted whole blood, and in EDTA and lithium heparin plasma than in serum at room temperature. Their recommendations are: 1. We recommend blood samples for PTH measurement should be taken into tubes containing EDTA and the plasma separated from the cells within 24 h of venepuncture	

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				[Strong recommendation]. This recommendation is consistent with guidance issued by the Clinical Laboratory Standards Institute (ref 1) and the World Health Organization (ref 2). 2. We recommend EDTA plasma samples for PTH measurement should be stored at 4°C and analysed within 72 h of venepuncture [Strong recommendation]. Ref 1: Clinical and Laboratory Standards Institute. Procedures for the handling and processing of blood specimens for common laboratory tests; approved guideline, 4th ed. Document H18-A4. Wayne, PA: Clinical and Laboratory Standards Institute, 2010:1–57. Ref 2: World Health Organization. Use of anticoagulants in diagnostic laboratory investigations and stability of blood, plasma and serum samples. WHO/DIL/LAB/99.1 Rev.2. Geneva: WHO, 2002:1–64. http://edqas.org/download/Preanalytical_PTH.pdf	
Hyperparathyroid UK Action 4 Change	Guideline	4	6 - 8	It is important to note that the EDTA vials must be filled completely. A potential explanation for iPTH sometimes rising in vials containing EDTA might be that those vials haven't been filled. Please see the following 2002 study: Preanalytical Factors in the Measurement of Intact Parathyroid Hormone with the DPC IMMULITE Assay: **http://clinchem.aaccjnls.org/content/48/3/566?ijkey=cf5813f4282ad20e98a62cd2e9136aa931448145&keytype2=tf_ipsecsha**	Thank you for your comment. As PTH is a relatively unstable element it is important that it is collected according to the relevant laboratory collection protocols. The method of collection was not identified as a topic for a review question by the committee. We have highlighted this topic with the surveillance review team so that they can search for evidence when it is published. This will be used to inform any update of this guideline.

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					The committee were aware that most laboratories specify EDTA blood collection tubes. However specifying the anticoagulant is not possible in the absence of a review question on this topic. We have added this detail to the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Guideline	4	7 - 11	1.1.5 PTH needs to be collected and stored correctly otherwise the sample degrades and could lead to a significant reduction in the reported PTH level. Vitamin D needs to be taken alongside PTH.	Thank you for your comment. As PTH is a relatively unstable element it is important that it is collected according to the relevant laboratory collection protocols. The method of collection was not identified as a topic for a review question by the committee. We have highlighted this topic with the surveillance review team so that they can search for evidence when it is published. This will be used to inform any update of this guideline. The committee were aware that most laboratories specify EDTA blood collection tubes. However specifying the anticoagulant is not possible in the absence of a review question on this topic. We have added this detail to the committee's discussion of the evidence in evidence report B. The committee agreed that measuring vitamin D and correcting any deficiency is essential in diagnosing and treating people with primary hyperparathyroidism, but noted that correcting a deficiency does not need to precede the diagnosis. We recognise the importance of correcting vitamin D deficiency, but for some primary care providers vitamin D testing is not available. This would slow down referrals from primary care, and can therefore be done in secondary care. This is fully discussed in evidence report B in the committee's discussion of the evidence.

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Hyperparathyroid UK Action 4 Change	Guideline	4	7 - 11	I would strongly recommend including the importance of testing parathyroid hormone (PTH) in EDTA rather than serum in order to obtain an accurate result especially if there is any chance the blood test will not be taken directly to the lab as PTH tested in serum is unstable and can result in a lower inaccurate result or a wasted test which is a waste of funds as well as leading to a possible misdiagnosis. It is worth noting here that doctors should be aware vitamin D, hypomagnesemia, unregulated glycaemic index and estrogen therapy can all lower PTH results, making it absolutely crucial to ensure PTH results are accurately tested to avoid the possibly of misdiagnosis.	Thank you for your comment. As PTH is a relatively unstable element it is important that it is collected according to the relevant laboratory collection protocols. The method of collection was not identified as a topic for a review question by the committee. We have highlighted this topic with the surveillance review team so that they can search for evidence when it is published. This will be used to inform any update of this guideline. The committee were aware that most laboratories specify EDTA blood collection tubes. However specifying the anticoagulant is not possible in the absence of a review question on this topic. We have added this detail to the committee's discussion of the evidence in evidence report B. We do recommend that calcium should be taken at the same time as PTH (recommendation 1.1.6). The committee therefore agreed that measuring vitamin D and correcting any deficiency is essential in diagnosing and treating people with primary hyperparathyroidism, but noted that correcting a deficiency does not need to precede the diagnosis. We recognise the importance of correcting vitamin D deficiency, but for some primary care providers vitamin D testing is not available. This would slow down referrals from primary care, and can therefore be done in secondary care. This is fully discussed in evidence report B in the committee's discussion of the evidence. Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function.

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					This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/ hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects on PTH secretion or function in PHPT. We have added this to the committee's discussion of the evidence in evidence report B. The committee discussed the other factors you have mentioned but in their knowledge and experience they do not have clinically important effects.
Hyperparathyroid UK Action 4 Change	Guideline	4	7-11	1.1.5 Parathyroid Hormone (PTH) should also be measured for anyone with symptoms of primary hyperparathyroidism whose calcium is within the normal range. If inappropriate relationship between pth and calcium is found, we should be diagnosed and treated for Normocalcemic Primary Hyperparathyroidism (NCPHPT).	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B. We have highlighted this topic with the surveillance review team so that any future updates of this guideline will incorporate new evidence when it becomes available.

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Hyperparathyroid UK Action 4 Change	Guideline	4	7 - 11	1.1.5 This does not take into consideration those with levels representing normocalcaemic phpt when adjusted calcium levels are below 2.5mmol/litre with an elevated PTH.	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B. We have highlighted this topic with the surveillance review team so that any future updates of this guideline will incorporate new evidence when it becomes available.
Hyperparathyroid UK Action 4 Change	Guideline	4	7 - 11	1.1.5 If a patient is continuing to experience symptoms of hyperparathyroidism, testing of calcium and PTH together should be offered regardless of the result of initial calcium test, as it is the inverse relationship between the two which provides a diagnosis. Current guidelines would mean those with normocalcaemic primary hyperparathyroidism would never be diagnosed. It is essential to also test magnesium, vitamin D and phosphate in order to make an educated diagnosis or in order to make an educated referral to either a	Thank you for your comment. Magnesium was not prioritised by the committee for inclusion in the review protocol. Magnesium could be an explanation for normocalcaemic PHPT but it is very rare and not a straightforward relationship. The committee recognises the importance of magnesium in calcium homeostasis, but magnesium is usually of relevance with low calcium (i.e. more relevant to hypocalcaemia not hypercalcaemia), but this was not prioritised during the scoping process. We have not made a recommendation not to check phosphate, but usually calcium and PTH would affect

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				hyperparathyroidism educated endocrinologist or experienced parathyroid surgeon.	phosphate rather than the other way round.
Hyperparathyroid UK Action 4 Change	Guideline	4	9 - 11	Lines 9 and 10 &11 are contradictory as patients with albumin-adjusted serum calcium of 2.6 mmol/litre of above on two separate occasions would also be suspected to have primary hyperparathyroidism.	Thank you for your comment. Your interpretation is consistent with the recommendation.
Hyperparathyroid UK Action 4 Change	Guideline	4	12	1.1.6 When testing PTH calcium and Vitamin D need doing at the same time to show if the correct suppressive relationship is in place.	Thank you for your comment. We do recommend that calcium should be taken at the same time as PTH (recommendation 1.1.6). The committee agreed that measuring vitamin D and correcting any deficiency is essential in diagnosing and treating people with primary hyperparathyroidism, but noted that correcting a deficiency does not need to precede the diagnosis. We recognise the importance of correcting vitamin D deficiency, but for some primary care providers vitamin D testing is not available. This would slow down referrals from primary care, and can therefore be done in secondary care. This is fully discussed in evidence report B in the committee's discussion of the evidence.
Hyperparathyroid UK Action 4 Change	Guideline	4	12	1.1.6 According to the Association of Clinical Biochemistry (whose recommendation for calcium levels the committee accept on p14 of the guidelines) PTH shows some diurnal variation and the ACB recommend that samples are obtained in the morning, preferably after an overnight fast. Why does the committee not follow the ACB guidelines for this?	Thank you for your comment. The committee in their experience stated that PTH testing can be done on a random sample, i.e. non-fasting and at any time of day. The committee considered that even though there is a marginal diurnal variation in PTH levels, it is not large enough to be adjusted for.
Hyperparathyroid UK Action 4 Change	Guideline	4	12	1.1.6 Given that the research on measurement of PTH in both serum and EDTA shows a considerable variation in results (up to 25%) the committee do not seem to have considered this aspect nor made recommendations	Thank you for your comment. As PTH is a relatively unstable element it is important that it is collected according to the relevant laboratory collection protocols. We have expanded the section on normocalcaemia in the committee's discussion of the

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				regarding PTH testing.	evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Guideline	4	12	1.1.6 When testing PTH, calcium and Vitamin D need to be tested from the same blood draw to determine a non/suppressive relationship between the calcium and parathyroid hormone. We believe it is vital to include in this guideline the role of parathyroid hormone, which is to regulate the level of calcium in the blood. Looking at one without the other is not conclusive. As vitamin D and magnesium can also impact the production of PTH, it is advisable to include these also to enable an educated starting point. If not already known, blood sugar should also be tested as uncontrolled glycaemic index can falsely lower PTH.	Thank you for your comment. We do recommend that calcium should be taken at the same time as PTH (recommendation 1.1.6). The committee therefore agreed that measuring vitamin D and correcting any deficiency is essential in diagnosing and treating people with primary hyperparathyroidism, but noted that correcting a deficiency does not need to precede the diagnosis. The committee recognises the importance of correcting vitamin D deficiency, but for some primary care providers vitamin D testing is not available. This would slow down referrals from primary care, and can therefore be done in secondary care. This is fully discussed in evidence report B in the committee's discussion of the evidence. Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function. This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects on PTH secretion or function in PHPT. We have added this to the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Guideline	4	14	1.1.7 We believe this line should be amended if magnesium has not been tested primarily to include*; 'if hypomagnesemia or magnesium below 0.8mmol/l has been excluded'*. An abstract from the following study should be taken into consideration when testing parathyroid hormone always; before and after	Thank you for your comment. Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function. This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/ hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have

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				surgery: *Critical to the regulation of mineral ion homeostasis is the inverse relationship between the extracellular calcium (Ca2+) concentration and PTH secretion (Fig. 1). Early studies in vivo [1] and in vitro [2] demonstrated that high magnesium (Mg2+) concentrations also inhibit PTH release. At low concentrations, on the other hand, the effects of Ca2+ and Mg2+ on PTH secretion differ: while hormonal secretion persists for an hour or more even at vanishingly low Ca2+ concentrations [3,4], Connie Anast and his co-workers were the first to demonstrate that low Mg2+ concentrations inhibit PTH secretion [5]. In these classical studies, Dr Anast was able to use detailed clinical observations in a single patient to draw important pathophysiological conclusions. Indeed, in the ensuing years, only limited progress has been made in extending these observations to elucidate the cellular mechanisms underlying the inhibition of PTH release at low Mg2+. Considerable advances, on the other hand, have been made in understanding the control of PTH release by high Ca2+ and Mg2+ concentrations. These studies will be reviewed here and provide, in turn, a conceptual framework within which to consider the effects of low Mg2+ on PTH secretion.* https://www.sciencedirect.com/science/article/pii/0169600989900032	material or clinically relevant effects on PTH secretion or function in PHPT. We have added this to the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Guideline	4	14	1.1.7 This is too dogmatic, It could potentially result in patients being denied repeat tests when doctors have not taken into	Thank you for your comment. The recommendations do not replace clinical judgement and repeat tests can be performed based on individual circumstances.

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				consideration the factors that can lower falsely lower PTH levels (serum tests, hypomagnesemia, estrogen replacement therapy and unregulated glycaemic index) and consequently refusing to refer them to secondary care.	
Hyperparathyroid UK Action 4 Change	Guideline	4	14	1.1.7 We are concerned that this recommendation has been made without consideration of magnesium and the effect on parathyroid hormone when magnesium is low or deficient and would recommend to always determine magnesium blood levels when testing parathyroid hormone. This study explains why: https://link.springer.com/article/10.1007%2FBF02408542 *'In a well-defined in vitro perifusion system, the effects of extracellular magnesium concentration (Mg) on parathyroid hormone (PTH) secretion by bovine parathyroid tissue were examined. At Mg less than 0.8 mM, the ability of the glands to secrete hormone maximally in response to low calcium (Ca) stimulation was progressively impaired. Low Mg also impaired the ability of isoproterenol, dibutyryl cyclic AMP and theophylline to stimulate hormone release. The defect in hormone release at low Mg observed in vitro was analogous to the well-documented inhibition of secretion observed in vivo. Increases in Mg from 0 to 0.8 mM rapidly repaired the defect in hormone secretion. At Mg above 1.0 mM there was a Ca-like effect on hormone release, with a progressive decrease in secretion at increased Mg. Although its mechanism is not yet clear, the*	Thank you for your comment. The committee did not prioritise magnesium in the review protocol. Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function. This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects on PTH secretion or function in PHPT. We have added this to the committee's discussion of the evidence in evidence report B.

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				low Mg effect appears to impair principally the process of hormone release rather than its biosynthesis or storage.	
Hyperparathyroid UK Action 4 Change	Guideline	4	14	1.1.7 To further reinforce the point above we would recommend a detail here referring to 'The Paradoxical Block of Parathyroid Hormone: https://www.ncbi.nlm.nih.gov/pubmed/11102444 *The paradox of blunted parathormone (PTH) secretion in patients with severe hypomagnesemia has been known for more than 20 years, but the underlying mechanism is not deciphered. We determined the effect of low magnesium on in vitro PTH release and on the signals triggered by activation of the calcium-sensing receptor (CaSR). Analogous to the in vivosituation, PTH release from dispersed parathyroid cells was suppressed under low magnesium. In parallel, the two major signalling pathways responsible for CaSR-triggered block of PTH secretion, the generation of inositol phosphates, and the inhibition of cAMP were enhanced. Desensitization or pertussis toxin-mediated inhibition of CaSR-stimulated signalling suppressed the effect of low magnesium, further confirming that magnesium acts within the axis CaSR-G-protein. However, the magnesium binding site responsible for inhibition of PTH secretion is not identical with the extracellular ion binding site of the CaSR, because the magnesium deficiency-dependent signal enhancement was not altered on CaSR*	Thank you for your comment. The recommendations specify what action should be taken and unfortunately it is not possible to refer to physiology of mechanisms of action in the recommendations. Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function. This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/ hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects on PTH secretion or function in PHPT. We have added this to the committee's discussion of the evidence in evidence report B. We have made the committee aware of this reference.

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				receptor mutants with increased or decreased affinity for calcium and magnesium. By contrast, when the magnesium affinity of the Gα subunit was decreased, CaSR activation was no longer affected by magnesium. Thus, the paradoxical block of PTH release under magnesium deficiency seems to be mediated through a novel mechanism involving an increase in the activity of Gα subunits of heterotrimeric G-proteins. (PDF) Paradoxical Block of Parathormone Secretion Is Mediated by Increased Activity of Gα Subunits. Available from: https://www.researchgate.net/publication/12226451_Paradoxical_Block_of_Parathormone_Secretion_Is_Mediated_by_Increased_Activity_of_Ga_Subunits	
Hyperparathyroid UK Action 4 Change	Guideline	4	14	1.1.7 This is obviously a cost issue, but I am sure the committee is aware that PTH produced by an enlarged parathyroid gland(s) or an adenoma is produced erratically, and one single measurement as advised might not be at its highest at one single blood draw. It is the same with calcium levels (which you have stated an awareness of on page 14, line 14) which can also fluctuate. It is worthwhile mentioning also that parathyroid hormone is naturally highest during sleeping hours and that modern practice no longer requires a fasting test but more often mid-morning to early afternoon. I believe most specialists would wish to see a trend for patients referred to them, so in our view this rather dogmatic instruction not to repeat PTH measurement in primary care should be removed.	Thank you for your comment. We have used the word 'routinely' to allow for repeat measurement if the clinical circumstances warrant this.

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Hyperparathyroid UK Action 4 Change	Guideline	4	14	1.1.7 To not routinely test PTH with calcium can lead to missed diagnosis when a patient demonstrates normal calcium with high PTH classified as Normocalcemic primary hyperparathyroidism	Thank you for your comment. We do recommend that PTH is tested with a concurrent calcium (recommendation 1.1.6).
Hyperparathyroid UK Action 4 Change	Guideline	4	14	1.1.7 We are concerned that putting this comment in the main guidelines will prevent patients being diagnosed sooner. The cost pf PTH testing could help diagnose patients sooner, this disease requires a number of tests to establish what is happening with the calcium and PTH correlation. Not just a stand-alone calcium test performed once or twice in primary care. Some areas already have a cost issue with vitamin D testing when investigating PHPT, resulting in GPs informing patients they are no longer allowed to order vitamin D tests due to costs.	Thank you for your comment. Recommendation 1.1.6 makes it clear that PTH should be measured concurrently with albumin-adjusted serum calcium. The committee agreed that measuring vitamin D and correcting any deficiency is essential in diagnosing and treating people with primary hyperparathyroidism, but noted that correcting a deficiency does not need to precede the diagnosis. The committee discussed that for some primary care providers, vitamin D testing is not universally available. They considered that measuring and correcting vitamin D levels before the diagnosis may slow down referrals from primary care, and hence agreed that this test should be performed in secondary care to facilitate a more timely diagnosis. The committee discussed that Vitamin D can affect the interpretation of the urinary calcium test, hence in people who are vitamin D deficient, the specialist should interpret the urine calcium with caution. However the likelihood of a urine calcium result being low is highly unlikely and the committee agreed this should not be a major feature of the diagnostic algorithm but when urine calcium is low, rarely, there is a major focus on ensuring vitamin D repletion. We have edited the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Guideline	4	14	1.1.7 Over a two year period, and repeated tests, my serum adjusted calcium has always been normal i.e. between 2.2 and 2.6 mmol/L,	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation

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				yet my PTH has fluctuated generally above the top of the PTH reference range. My Vitamin D has been normal and all other factors relating to secondary hyperparathyroidism excluded. I clearly have normocalcaemic hyperparathyroidism yet this draft guideline fails to address my situation and those of many others in the same situation. My case is not an isolated incident.	1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B. We have highlighted this topic with the surveillance review team so that any future updates of this guideline will incorporate new evidence when it becomes available.
Hyperparathyroid UK Action 4 Change	Guideline	4	14	1.1.7 There are many people in our group diagnosed with normocalcaemic hyperparathyroidism (NCPHPT) in the UK and globally, who have benefitted from surgery. This guideline makes no account of NCPHPT, and does not consider practices outside of the UK who are far more advanced than us. The UK needs to become as aware as our international peers, and indeed some highly regarded UK parathyroid surgeons, and adopt their advanced knowledge and methods of addressing NCPHPT in order to restore quality of life to patients and save decades of unnecessary, costly treatment for untreated	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have

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				normocalcemic primary hyperparathyroidism.	expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B. We have highlighted this topic with the surveillance review team so that any future updates of this guideline will incorporate new evidence when it becomes available.
Hyperparathyroid UK Action 4 Change	Guideline	4	15	1.1.8 Also If the correct suppressive relationship is not in place but the individual readings are within normal ranges.	Thank you for your comment. Recommendation 1.1.8 covers the majority of presentations of PHPT including people with a calcium of 2.5 mmol/litre and a PTH above the mid-point of the normal range.
Hyperparathyroid UK Action 4 Change	Guideline	4	15	1.1.8 For an area that is not at all well understood by endocrinologists this provides no meaningful guidance or substance. Patients are simply told to seek specialist advice. Herein lies the problem; there aren't enough specialists who understand these nuances of high PTH and normal calcium or high calcium and normal PTH. The objective here should be that these guidelines should provide a steer to those medical specialists who do not have much experience of dealing with such cases.	Thank you for your comment. The committee recognised that people can experience a delay in diagnosis and we expect that the recommendations on when to test and what action to take based on the results will improve this. These recommendations do not replace clinical judgement and we would encourage a GP for example to discuss people with the results you describe with a specialist.
Hyperparathyroid UK Action 4 Change	Guideline	4	15 - 16	1.1.8 At the same time as seeking specialist advice, request a DXA (dual-energy X-ray absorptiometry) scan of the lumbar spine, hip and distal radius forearm to determine bone density.	Thank you for your comment. A DXA would be ordered after a diagnosis of PHPT has been made; this could be after seeking specialist advice but before the appointment with the specialist.
Hyperparathyroid UK Action 4 Change	Guideline	4	15 - 19	*1.1.8 Seek specialist advice if:* • *PTH is above the midpoint of the reference range and primary hyperparathyroidism is suspected or* • *PTH is below the midpoint of the reference*	Thank you for your comment. Recommendation 1.1.5 specifies a threshold for PTH testing and the others quoted lower down are in the threshold for diagnosis. Very low serum magnesium can suppress PTH

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			20 - 24	*range and the concurrent albumin-adjusted serum calcium level is 2.6 mmol/litre or above*. *Do not offer further investigations for primary hyperparathyroidism if:* • *PTH is within the reference range but below the midpoint of the reference range and* • *the concurrent albumin-adjusted serum calcium level is 2.6 mmol/litre.* Both of the above recommendations contradict the level stated on page 4 line 10, of 2.50mmol/l. It is important to rule out hypomagnesemia when testing PTH because it could be below mid-point as a direct result of The Paradoxical Block of PTH Secretion', which would need correcting to determine a true PTH level therefore contradicting your recommendation on line 20. Not testing magnesium could result in misdiagnosis. http://www.jbc.org/content/276/9/6763.full	secretion and also cause resistance to PTH function. This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/ hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects on PTH secretion or function in PHPT. We have added this to the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Guideline	4	16	1.1.8 Reference range varies in labs-my own GP not aware of that and input my hospital labs as normal due to being reported in a different range. They did not convert to the range their GP lab uses and see how it was actually abnormal. The guidelines for primary care need to be clearer in the possibility of different ranges used.	Thank you for your comment. The committee noted that the reference range for PTH varies from laboratory to laboratory, so numerical thresholds cannot be specified in the recommendation.
Hyperparathyroid UK Action 4 Change	Guideline	4	16 - 19	1.1.8 PTH needs to be measured in EDTA vials. If, as happens now, some NHS Trust labs test PTH in serum and not EDTA the results will be different in different parts of the country and PHPT diagnosis will be a postcode lottery. In my area (Torbay and South Devon), the lab uses the serum vials which	Thank you for your comment. As PTH is a relatively unstable element it is important that it is taken according to the relevant laboratory collection protocols. Different approaches to PTH measurement were not prioritised during as a review question. We have highlighted this topic with the surveillance review team

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				means the PTH is unstable and degenerates if not tested immediately. Testing should be standardised across the country so that all labs use EDTA for PTH testing. I noted that it was stated that ionised calcium should not be used as a measurement because testing was so variable – at the moment PTH testing is also equally variable and needs to be standardised.	so that they can search for evidence when it is published. This will be used to inform any update of this guideline. The committee were aware that there are a number of approaches to PTH measurement and most laboratories specify EDTA blood collection tubes. We have added this detail the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Guideline	4	18 - 19	1.1.8 Please note that lines 18-19 contradict line 10*: 2.5 mmol/litre or above on at least 2 separate occasions*. Line 19 says *concurrent albumin-adjusted serum calcium level is 2.6 mmol/litre or above* instead of 2.5 which is misleading and confusing. It should be 2.5mmol/litre to concur with line 10. A PTH above midpoint with a calcium above 2.5mmol/litre is indicative or Primary Hyperparathyroidism. It is well established that the level of calcium does not determine the severity of symptoms of primary hyperparathyroidism so this a very important factor to establish in this guideline.	Thank you for your comment. We do not believe they are contradictory as recommendation 1.1.5 specifies a threshold for PTH testing and the others quoted lower down are thresholds for diagnosis.
Hyperparathyroid UK Action 4 Change	Guideline	4	18 - 19	1.1.8 Recommendations again refer to 2.6 as the 'magic number' for calcium when PTH is above or below the midpoint. This does not relate to an individual's own set point. The recommendations attempt to address this but do not take account of the true suppression curve and set point that should be considered.	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data

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					was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B. We have highlighted this topic with the surveillance review team so that any future updates of this guideline will incorporate new evidence when it becomes available.
Hyperparathyroid UK Action 4 Change	Guideline	4	20	1.1.9 PTH is often stored/transported incorrectly and not in EDTA tubes. It also has a short half-life. On this basis further investigations should not be curtailed just because PTH is below midpoint of ref range	Thank you for your comment. As PTH is a relatively unstable element it is important that it is taken according to the relevant laboratory collection protocols. Different approaches to PTH measurement were not raised during scoping as a review question. The committee were aware that there are a number of approaches to PTH measurement and most laboratories specify EDTA blood collection tubes. We have added this detail the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Guideline	4	20	1.1.9 This guideline denies the existence of normohormonal primary hyperparathyroidism for those patients that have a calcium set point that does not follow the normal distribution curve. If all reasons for hypercalcaemia can be ruled out other than hyperparathyroidism, then what is the patient supposed to do?	Thank you for your comment. The committee's definition of PHPT that is used in the guideline does not preclude people with PTH below mid-range being diagnosed with PHPT. Recommendation 1.1.8 – 'Seek specialist advice from a specialist with expertise in primary hyperparathyroidism if their PTH measurement is… below the midpoint of the reference range with a concurrent albumin-adjusted serum calcium level of 2.6 mmol/litre or above - includes people with normohormonal PHPT. In this case the GP would perform the PTH test after the second calcium test and given the combination of results would then seek

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					specialist advice.
Hyperparathyroid UK Action 4 Change	Guideline	4	20	1.1.9 This instruction will ensure that patients with normocalcemic PHPT are missed, which was perhaps the intention. However, we know from the **London Endocrine Centre** that *"Patients with normocalcemic hyperparathyroidism are normocalcemic but with a consistently inappropriately elevated PTH in the absence of secondary causes of hyperparathyroidism ... there is a suggestion that it may be present in the earliest form of pHPT, a phase characterised by elevated PTH that leads to a reduced cortical bone density but without hypercalcemia."*	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B. We have highlighted this topic with the surveillance review team so that any future updates of this guideline will incorporate new evidence when it becomes available.
Hyperparathyroid UK Action 4 Change	Guideline	4	20	1.1.9 J P Bilezikian and S J Silverberg, who have been responsible for much PHPT research in the past, state in their 2010 paper Normocalcemic Hyperparathyroidism that *"We may now be entering a 3rd era in the history of this disease in which patients are being discovered with normal total and ionized serum calcium concentrations but with parathyroid levels that are consistently elevated. In this article, we describe this new entity, normocalcemic primary hyperparathyroidism, a*	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified

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				forme frust of the disease." See also: Richard Eastell et al, 2014: Diagnosis of Asymptomatic Primary Hyperparathyroidism: Proceedings of the Fourth International Workshop which states: *"We conclude that ... 3) normocalcemic PHPT is a variant of the more common presentation of PHPT with hypercalcemia ..."* See also: N Garcia de la Torre, J A H Wass and H E Turner's Review dated 2003 entitled Parathyroid adenomas and cardiovascular risk, *the abstract of which states:* *"In recent decades, primary hyperparathyroidism (pHPT) has changed its clinical presentation from a disease with bone and renal involvement to a frequently asymptomatic disorder detected on routine biochemistry. Nevertheless, it remains unclear whether patients with untreated mild asymptomatic hyperparathyroidism are at risk for other complications such as increased morbidity and mortality from cardiovascular diseases..... cure of pHPT does not lead to improvement of the cardiovascular disorder e.g. hypertension."* On this topic see also the paper by Rachel K Crowley, Neil J Gittoes, Clin Endocrinol 2016, entitled Elevated PTH with Normal Serum Calcium Level, A Structured Approach which states: *"Apart from bone and renal health, there is some evidence that normocalcemic PHPT is*	through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B. We have highlighted this topic with the surveillance review team so that any future updates of this guideline will incorporate new evidence when it becomes available.

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				associated with an increased risk of hypertension. Therefore, normocalcemic PHPT cannot be considered to have a completely benign clinical course ...."	
Hyperparathyroid UK Action 4 Change	Guideline	4	20	1.1.9 In view of the UK Government's longstanding attempts to alleviate the burden of **cardiovascular disease** on both NHS services and on patients themselves, it might be prudent to ensure that any form of PHPT is treated promptly in its early stages. This is one reason amongst many, why I do not think that the issue of normocalcemic PHPT can be omitted from these guidelines, given the elapsed time since these papers were published. Our stakeholder group has many members who have had successful PTH surgery and were originally diagnosed as having normocalcemic PHPT by enlightened endocrinologists and surgeons. The latter will remain in a distinct minority however until acknowledgement of normocalcemic PHPT becomes mainstream, and these guidelines should be addressing that. **Quality of Life** is mentioned several times in these guidelines, but if normocalcemic PHPT is not covered here then the QOL of a large proportion of PHPT patients will clearly be further adversely affected, with all the attendant costs involved.	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B. We have highlighted this topic with the surveillance review team so that any future updates of this guideline will incorporate new evidence when it becomes available.
Hyperparathyroid UK Action 4 Change	Guideline	4	20 - 22	1.1.9 It is our opinion based on experience from members in our organisation that Normohormonal primary hyperparathyroidism (NHPHPT) is the third classification of primary hyperparathyroidism that must be included in	Thank you for your comment. The committee's definition of PHPT that is used in the guideline does not preclude people with PTH below mid-range being diagnosed with PHPT.

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				this guideline. We have members who can provide clinical case stories with biochemical results as evidence at request. Please read this 2011 study. Here is an extract: While normocalcemic hyperparathyroidism is well recognised in primary hyperparathyroidism (PHP), less is known about patients with high calcium but normal intact parathyroid hormone (iPTH). We aimed to describe this entity and designated it normohormonal primary hyperparathyroidism (NHPHP): https://www.sciencedirect.com/science/article/pii/S0039606011005253 *Results: NHPHP occurred in 46 of 843 patients (5.5%) undergoing initial parathyroidectomy for PHP. All had hypercalcemia (11.1 mg/dL). Regarding preoperative iPTH, 7 patients (15%) had values <40 pg/mL, 19 (41%) had values <60 pg/mL; and 20 (44%) had intermittent values >60 pg/mL. Unlike patients with elevated iPTH, nearly all NHPHP patients had additional testing delaying the operation. Imaging correctly localized NHPHP parathyroid disease in 80%. At the time of operation, 74% of NHPHP patients had single adenomas. Intraoperatively postmobilization, using the same assay that was used preoperatively, 82% had PTH levels >60 pg/mL (mean, 279 pg/mL). During the follow-up period, iPTH levels remained lower among NHPHP patients (21 pg/mL) compared to 41 pg/mL for patients with preoperative iPTH 60 to 100 pg/mL and 56 pg/mL for patients with preoperative iPTH 100*	Recommendation 1.1.8 – 'Seek advice from a specialist with expertise in primary hyperparathyroidism if their PTH is below the midpoint of the reference range with a concurrent albumin-adjusted serum calcium level of 2.6 mmol/litre or above' - includes people with normohormonal PHPT. In this case the GP would perform the PTH test after the second calcium test and given the combination of results would then seek specialist advice.

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				to 200 pg/mL (P < .0001). *Conclusion: Lower PTH set points may exist in some patients with otherwise typical PHP features. Although high normal iPTH is inappropriate for hypercalcemia and should suggest PHP, this disorder may occur with iPTH levels as low as 5 pg/mL. Awareness of the unusual phenotype of NHPHP may facilitate earlier diagnosis and surgery.*	
Hyperparathyroid UK Action 4 Change	Guideline	4	20 - 22	1.1.9 We are concerned this recommendation is misleading without including a recommendation that a symptomatic patient (referring to symptoms we have listed in 1.1.1), could have a lower than expected iPTH level based on several factors. It is important that a diagnosis of NHPHPT should not be excluded without validating the following factors have been excluded, as any or all of them could contribute to a lower than expected iPTH result: 1) at venepuncture, the blood was taken into serum vacutainer rather than EDTA, and kept at room temperature for more than 30 minutes. 2) Hypomagnesemia has been ruled out. 3) An uncontrolled glycaemic index has been ruled out. 4) Is the patient on HRT?	Thank you for your comment. The committee's definition of PHPT that is used in the guideline does not preclude people with PTH below mid-range being diagnosed with PHPT. Recommendation 1.1.8 – 'Seek advice from a specialist with expertise in primary hyperparathyroidism if their PTH measurement is… below the midpoint of the reference range with a concurrent albumin-adjusted serum calcium level of 2.6 mmol/litre or above' - includes people with normohormonal PHPT. In this case the GP would perform the PTH test after the second calcium test and given the combination of results would then seek specialist advice.
Hyperparathyroid UK Action 4 Change	Guideline	4	20 - 22	1.1.9 Please read this study about NHPHPT and be aware that 22.5% of the parathyroid population have normohormonal primary hyperparathyroidism. '*Normohormonal primary hyperparathyroidism is a distinct form of primary hyperparathyroidism'* https://www.sciencedirect.com/science/article/pii/S0039606016305190	Thank you for your comment. The committee's definition of PHPT that is used in the guideline does not preclude people with PTH below mid-range being diagnosed with PHPT. Recommendation 1.1.8 – 'Seek advice from a specialist with expertise in primary hyperparathyroidism if their PTH measurement is… below the midpoint of the reference range with a

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					concurrent albumin-adjusted serum calcium level of 2.6 mmol/litre or above' - includes people with normohormonal PHPT. In this case the GP would perform the PTH test after the second calcium test and given the combination of results would then seek specialist advice.
Hyperparathyroid UK Action 4 Change	Guideline	4	20 - 24	1.1.9 You have contradicted line 10 which recommends testing *PTH for people whose albumin-adjusted serum calcium level is 2.5 mmol/litre or above on at least 2 separate occasions and primary hyperparathyroidism is suspected,* only to recommend on line 20-24*: Do not offer further investigations for primary hyperparathyroidism if PTH is within the reference range but below the midpoint of the reference range and the concurrent albumin-adjusted serum calcium level is below 2.6 mmol/litre. This is misleading, I recommend that you are consistent throughout the guideline with albumin adjusted serum calcium level of 2.5mmol/litre. It is also crucial to notify here for the patient suspected of having primary hyperparathyroidism, and to avoid a misdiagnosis, that their PTH can be lowered by several factors; inaccurate test conditions such as non edta samples left at room temperature, hypomagnesemia and poor glycaemic control. These factors need to be ruled out before dismissing a diagnosis for a symptomatic patient. Patient studies and evidence can be provided and are available to confirm these facts.*	Thank you for your comment. The two statements are not contradictory. The first statement is giving advice about when to test for primary hyperparathyroidism by doing a PTH test. The lower statement is what to when the PTH test result is known. The flexibility in interpretation of the PTH result in 1.1.8, which allows for the diagnosis of primary hyperparathyroidism in the presence of a PTH level below the mid-point of the reference range.
Hyperparathyroid UK Action 4 Change	Guideline	4	23	1.1.9 Using the level of adjusted serum Ca of 2.6 and above will exclude diagnosis of those with inappropriately raised PTH,	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation

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				normocalcaemic primary hyperparathyroidism and also those where a second adenoma is developing.	1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B. We have highlighted this topic with the surveillance review team so that any future updates of this guideline will incorporate new evidence when it becomes available. .
Hyperparathyroid UK Action 4 Change	Guideline	5	2 - 3	1.1.11 These lines recommend to correct Vitamin D levels. Despite maximum Vitamin D supplementation, my levels over several years have only moved from severely deficient to deficient. Further advice is required in these circumstances regarding adding magnesium supplementation and if still not corrected, seeking to understand why body is not attaining or maintaining appropriate Vit D levels.	Thank you for your comment. Vitamin D management was outside of the scope of this guideline. Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function. This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects on PTH secretion or function in PHPT. We have added this to the committee's discussion of the evidence in evidence report B.

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Hyperparathyroid UK Action 4 Change	Guideline	5	2 - 3	1.1.11 Some GP's cannot order vitamin D tests. An explanation of why vitamin D needs to be tested at least periodically alongside calcium and PTH especially in the instance of a first test to gain a clear picture, and again a few weeks after initiating vitamin D supplements, should be in these guidelines as either common sense is not prevailing or finance limitations are preventing common sense tests from prevailing. It is not acceptable to be told well everyone will benefit from vitamin D in the winter months, when a diagnosis for primary hyperparathyroidism is the main objective.	Thank you for your comment. Vitamin D management was outside of the scope of this guideline. We have added 'in secondary care' to the heading of the section for the recommendation on vitamin D testing.
Hyperparathyroid UK Action 4 Change	Guideline	5	2 - 3	No reference to testing Magnesium levels, essential for the absorption of and metabolism of Vitamin D. See review published in March 2018 in the Journal of the American Osteopathic Association. This review presented the biological significance of magnesium in vit D metabolism and its therapeutic importance to minimise complications related to vit D deficiency. https://www.researchgate.net/publication/323444405_Role_of_Magnesium_in_Vitamin_D_Activation_and_Function	Thank you for your comment. Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function. This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects on PTH secretion or function in PHPT. We have added this to the committee's discussion of the evidence in evidence report B. Magnesium supplementation was not prioritised by the committee as a review question.
Hyperparathyroid UK Action 4 Change	Guideline	5	2 - 3	1.1.11 Caution should be taken when correcting a vitamin D deficiency in patients with primary hyperparathyroidism. Prescribing large doses will likely result in hypomagnesemia or worsening hypomagnesemia if already evident. RBC magnesium should always be tested with vitamin D and consideration taken that magnesium is almost certainly needed to	Thank you for your comment. In the committee's discussion of the evidence in evidence report B we discuss that it is safe to correct any vitamin D deficiency. In the knowledge and experience of the committee and based on research vitamin D repletion in patients with primary hyperparathyroidism does not exacerbate hypercalcemia and may decrease levels of PTH and bone turnover.

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				successfully correct a vitamin D deficiency which will most likely be corrected with fewer symptoms using a smaller daily dose than a large weekly dose. Magnesium deficiency can also be responsible for a blunted PTH response in established osteoporosis, so it is wise to consider magnesium alongside vitamin D, calcium and PTH when looking to make an educated diagnosis of primary hyperparathyroidism. Please look at this article taken from Osteoporosis International regarding a magnesium loading test for vitamin D deficiency and blunted PTH response: https://link.springer.com/article/10.1007/s00198-006-0084-3	The management of vitamin D was outside of the scope of this guideline. Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function. This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects on PTH secretion or function in PHPT. Magnesium supplementation was not prioritised by the committee as a review question. We have added this to the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Guideline	5	2 - 3	*"Magnesium deficiency shuts down the vitamin D synthesis and metabolism pathway" https://www.fabresearch.org/viewItem.php?id=12315&listId=341&categoryId=&navPageId=342&utm_source=MadMimi&utm_medium=email&utm_content=Keep+up+with+the+latest+food+and+behaviour+news+throughout+2019&utm_campaign=20190103_m149066628_0035+03+January+2019&utm_term=Study+shows+magnesium+optimizes+vitamin+D+status* There is so much information available about the necessity for magnesium for vitamin D homeostasis, we expect all our doctors to know but are frankly astonished at the lack of knowledge by doctors, who are prescribing huge doses of vitamin D and not understanding why their patients are unable to	Thank you for your comment. Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function. This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects on PTH secretion or function in PHPT. Magnesium supplementation was not prioritised by the committee as a review question. We have added this to the committee's discussion of the evidence in evidence report B.

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				increase their levels. Please read these studies and make a recommendation to always recommend magnesium with vitamin D supplements and to test RBC magnesium and/or 24 hour urinary magnesium when testing vitamin D.	
Hyperparathyroid UK Action 4 Change	Guideline	5	2 - 3	1.1.11 https://medicalxpress.com/news/2018-02-magnesium-vitamin-d-ineffective.html This article from February 2018 is based on a research study which emphasises the point we are trying to make about why magnesium should always be considered when testing and prescribing vitamin D before and after surgery: *A review published in The Journal of the American Osteopathic Association found Vitamin D can't be metabolized without sufficient magnesium levels, meaning Vitamin D remains stored and inactive for as many as 50 percent of Americans. "People are taking Vitamin D supplements but don't realize how it gets metabolized. Without magnesium, Vitamin D is not really useful or safe," says study co-author Mohammed S. Razzaque, MBBS, PhD, a professor of pathology at Lake Erie College of Osteopathic Medicine.*	Thank you for your comment. Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function. This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects on PTH secretion or function in PHPT. Magnesium supplementation was not prioritised by the committee as a review question. We have added this to the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Guideline	5	2 - 3	*'Because serum magnesium does not reflect intracellular magnesium, the latter making up more than 99% of total body magnesium, most cases of magnesium deficiency are undiagnosed. Furthermore, because of chronic diseases, medications, decreases in food crop magnesium contents, and the availability of refined and processed foods, the vast majority of people in modern societies are at risk for magnesium deficiency. Certain individuals will*	Thank you for your comment. Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function. This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/ hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects on PTH secretion or function in PHPT.

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				need to supplement with magnesium in order to prevent suboptimal magnesium deficiency, especially if trying to obtain an optimal magnesium status to prevent chronic disease. Subclinical magnesium deficiency increases the risk of numerous types of cardiovascular disease, costs nations around the world an incalculable amount of healthcare costs and suffering, and should be considered a public health crisis. That an easy, cost-effective strategy exists to prevent and treat subclinical magnesium deficiency should provide an urgent call to action' *Please read this study and be as aware of the importance of magnesium as we are, and include a recommendation for magnesium in this guideline. Certain types of magnesium are beneficial while others are mostly a laxative which we do not recommend.* *https://openheart.bmj.com/content/5/1/e000668*	We have added this to the committee's discussion of the evidence in evidence report B. Magnesium supplementation was not prioritised by the committee as a review question.
Hyperparathyroid UK Action 4 Change	Guideline	5	2 - 3	1.1.11 We recommend an inclusion of magnesium whenever supplementing with vitamin D. We are extremely aware of a lack of knowledge across the board between primary and secondary care regarding the combined role of magnesium, vitamin D, calcium and parathyroid hormone; *This study confirms that in patients with established osteoporosis, there is also a distinct group with a low vitamin D and a blunted PTH level and that Mg deficiency (as measured by the Mg loading test) is an important contributing factor : https://link.springer.com/article/10.1007/s0019*	Thank you for your comment. We do recommend that calcium should be taken at the same time as PTH (recommendation 1.1.6). The committee agreed that measuring vitamin D and correcting any deficiency is essential in diagnosing and treating people with primary hyperparathyroidism, but noted that correcting a deficiency does not need to precede the diagnosis. The committee recognises the importance of correcting vitamin D deficiency, but for some primary care providers vitamin D testing is not available. This would slow down referrals from primary care, and can therefore be done in secondary care to

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				8-006-0084-3	facilitate a more timely diagnosis. The committee discussed that Vitamin D can affect the interpretation of the urinary calcium test, hence in people who are vitamin D deficient, the specialist should interpret the urine calcium with caution. However the likelihood of a urine calcium result being low is highly unlikely and the committee agreed this should not be a major feature of the diagnostic algorithm but when urine calcium is low, rarely, there is a major focus on ensuring vitamin D repletion. We have edited the committee's discussion of the evidence in evidence report B to include this detail. Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function. This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects on PTH secretion or function in PHPT.
Hyperparathyroid UK Action 4 Change	Guideline	5	2 - 3	1.1.11Caution needs to be taken when prescribing large doses of vitamin D to a patient with primary hyperparathyroidism as it may cause calcium levels to rise further and therefore exacerbate already debilitating symptoms.	Thank you for your comment. The correction of vitamin D was not prioritised during the scoping process of this guideline.
Hyperparathyroid UK Action 4 Change	Guideline	5	2 - 3	1.1.11 Trying to rectify Vitamin D should not be undertaken for longer than a few months without monitoring adjusted serum calcium levels. It may further elevate serum calcium levels, exacerbating symptoms in some patients	Thank you for your comment. The correction of vitamin D deficiency was not prioritised during the scoping process of this guideline.
Hyperparathyroid UK Action 4 Change	Guideline	5	2 - 3	1.1.11 This 2018 article discusses the link with vitamin D deficiency and depression in adults,	Thank you for your comment. Vitamin D management was outside of the scope of this guideline.

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				after 4 years. As depression is a symptom within over 90% of our members, we agree it is very important to try to raise vitamin D to a healthy level > 75, but it is crucial to always recommend taking it with magnesium and to avoid the brand containing the blue dye Butylated hydroxytoluene (BHT); a lab-made chemical that is added to foods as a preservative. There is evidence it causes cell division; http://ukfoodguide.net/e321.htm	Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function. This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects on PTH secretion or function in PHPT. We have added this to the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Guideline	5	2 - 3	1.1.11 Although many with primary hyperparathyroidism will have a vitamin D deficiency, and should indeed aim to increase their levels to above 75, it would be very helpful to advise small daily doses taken with magnesium is a more successful approach than large doses which can result in hypomagnesemia and worsening symptoms,	Thank you for your comment. We recognise the importance of correcting vitamin D deficiency and in the committee's discussion of the evidence we discuss that it is safe to correct any vitamin D deficiency. Vitamin D management was outside of the scope of this guideline.
Hyperparathyroid UK Action 4 Change	Guideline	5	2 - 3	1.1.11 Some patients have worsening symptoms when given large doses of vitamin D and people should be carefully monitored with repeat tests advised and hydration advised.	Thank you for your comment. We recognise the importance of correcting vitamin D deficiency and in the committee's discussion of the evidence we discuss that it is safe to correct any vitamin D deficiency. Vitamin D management was outside of the scope of this guideline.
Hyperparathyroid UK Action 4 Change	Guideline	5	2 - 3	1.1.11 People on Vitamin D supplementation pre-op require regular monitoring as Vitamin D does not suit everyone pre op and can cause the already high calcium to rise exacerbating the condition. Some people in our group have had to go to A&E as it made them so ill. This is costly to them and the NHS.	Thank you for your comment. We recognise the importance of correcting vitamin D deficiency and in the committee's discussion of the evidence we discuss that it is safe to correct any vitamin D deficiency. Vitamin D management outside of the scope of this guideline.
Hyperparathyroid UK Action 4 Change	Guideline	5	5 - 7	1.1.12: Fasting urinary fractional excretion index is probably the best and easiest to	Thank you for your comment. The diagnosis of familial hypocalciuric hypercalcaemia was not prioritised

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				perform, test to exclude FHH, though I agree the others are options.	during the scoping process of this guideline. We looked at evidence for the screening tests but only identified one study. All 3 tests were very similar in terms of diagnostic accuracy. We were therefore unable to recommend one test over another. Fasting urinary fractional excretion was not included in the evidence review protocol for this review question.
Hyperparathyroid UK Action 4 Change	Guideline	5	5 - 7	1.1.12 When testing to exclude familial hypercalciuria hypercalcaemia (FHH), what do you recommend if one of the tests offered to a patient is not conclusive? Should they then be offered another of the three tests or are you saying that any one of those tests will always prove conclusive to exclude familial hypercalciuria hypercalcaemia? This needs to be clarified.	Thank you for your comment. The diagnosis of familial hypocalciuric hypercalcaemia was not prioritised during the scoping process of this guideline. We looked at evidence for the screening tests but only identified one study. All 3 tests were very similar in terms of diagnostic accuracy. We were therefore unable to recommend one test over another. Cut-offs for these tests are determined locally.
Hyperparathyroid UK Action 4 Change	Guideline	5	8	1.1.12 Undertaking a 24 hr urine calcium may procure a diagnosis for those with marked hypercalciuria.	Thank you for your comment. There was no evidence to recommend one of the three tests of over the other and therefore any of the tests can be carried out. Evidence review B does not focus on the diagnosis of familial hypocalciuric hypercalcaemia. The diagnosis of FHH was not prioritised during the scoping process of this guideline.
Hyperparathyroid UK Action 4 Change	Guideline	5	12 - 18	1.1.13 It is not always possible to confirm a diagnosis on the basis of serum adjusted calcium and PTH alone where calcium is within the normal range and PTH is high. Consequently; assess symptoms and comorbidities, measure EGFR (estimated glomerular filtration rate) or serum creatinine, a DXA (dual-energy X-ray absorptiometry) scan of the lumbar spine, distal radius and hip. An ultrasound scan of the renal tract, should also be recommended. They all help build a clear	Thank you for your comment. People who have signs of end organ disease would have their calcium measured (recommendation 1.1.1). In the knowledge and experience of the committee a diagnosis of PHPT can be made based on albumin-adjusted serum calcium and PTH.

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				picture and reduce the reliance placed on blood tests when a diagnosis is not clear cut.	
Hyperparathyroid UK Action 4 Change	Guideline	5	16 - 17	1.1.13 Specifically, the DXA scan should be of the distal radius in the non-dominant forearm, unless there has been a previous fracture in this bone which may skew results.	Thank you for your comment. We have specified the distal radius in recommendation 1.2.3 but the evidence did state if it should be the dominant or non-dominant forearm.
Hyperparathyroid UK Action 4 Change	Guideline	5	20	1.2.1 We would it to be made clear that we can choose who we are referred to and/or request a 2nd referral. We should be involved in choosing our surgeon. We know only too well that not all head and neck surgeons have this expertise?	Thank you for your comment. The NICE guideline on Patient Experience in adult NHS services (CG138) makes recommendations on requesting a second opinion. We refer to this guideline in evidence report K.
Hyperparathyroid UK Action 4 Change	Guideline	5	21 - 22	1.2.1 Surgery should be performed by surgeons specialising in parathyroid surgery, ideally 50+ surgeries per year. We are aware of exceptionally good surgeons who have performed less to date, it is recommended primary care take this into consideration and the patient should have confidence in the surgeon they are referred to We would recommend it be made clear that we can choose who we are referred to and/or request a 2nd referral. We should be involved in choosing our surgeon. We know only too well that not all head and neck surgeons have this expertise	Thank you for your comment. It is outside of the remit of this guideline to define what expertise a surgeon should have.
Hyperparathyroid UK Action 4 Change	Guideline	5	21 - 22	Again, the symptoms of anxiety, depression, fatigue or atrial fibrillation are not mentioned here. However, lines 21-22 should simply read 'Refer people with primary hyperparathyroidism to a surgeon experienced in parathyroid surgery.' Surgery is the only cure, and delaying surgery post diagnosis only leads to further development of symptoms, a	Thank you for your comment. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is

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				poorer quality of life, and the extra cost of attempting to manage symptoms until inevitably surgery is required. Leaving this for GPs to 'consider' (page 6 line 1) leaves patients vulnerable to GP's discretion	less certain. The committee did agree that surgery may benefit people without the symptoms identified in 1.3.1 but the benefit it less certain than for people with the symptoms.
Hyperparathyroid UK Action 4 Change	Guideline	5	21 - 26	1.2.1 This should also include high PHT level with corresponding calcium within the normal range as it currently excludes all patients with normocalcemic primary hyperparathyroidism. Please read this link from The World journal of Surgery first published January 2018. Its title is: Classic Primary Hyperparathyroidism Versus Normocalcemic and Normohormonal Variants: Do They Really Differ? These guidelines must be altered accordingly: https://link.springer.com/article/10.1007%2Fs00268-018-4512-2	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B. We have highlighted this topic with the surveillance review team so that any future updates of this guideline will incorporate new evidence when it becomes available. We have made the committee aware of the reference.
Hyperparathyroid UK Action 4 Change	Guideline	5	21 - 26	The **use of calcium levels >2.85mmol/L as one of the criteria for referral for surgery** needs to be removed, particularly since Evidence C (Page 24, lines 7-9) used by the committee to determine this criteria states *"there is no evidence to support a particular cut-off point for adjusted serum calcium*	Thank you for your comment. The two recommendations for surgery in section 1.3 need to considered as a pair, not in isolation of each other. This guideline is extending the indications for surgery in that **all** patients with primary hyperparathyroidism are eligible for surgery in this guideline. The difference between 1.3.1 (offer) and 1.3.2 (consider) is that the

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				requiring surgery". This seems to have been idly included based on historical use, rather than due to clinical relevance or importance to determine eligibility for referral for surgery. In addition, the obvious unpredictability of abnormal serum calcium levels in patients with parathyroid disease is not mentioned in the draft guidelines. It should be noted that calcium levels do not rise as the disease progresses, nor are symptoms fewer for those patients with lower abnormal levels of serum calcium, as many medical professionals currently seem to believe (and which would unfortunately prevail if this non-evidenced based information is included in the final guidelines). Serum calcium levels in PHPT patients are unpredictable, persistently going up and down, within a usually tightly-controlled range. A diseased parathyroid gland that is unable to work correctly can only produce **unpredictable** adjusted serum calcium results. It is wrong to assume or imply that the level of adjusted serum calcium increases, ascends, has any predictable course, or is higher in patients requiring surgery than those who have levels between 2.6-2.85mmol/L. It is therefore completely incorrect to assume or imply that higher serum calcium levels (>2.85mmol/L) are a predictor of whether a patient requires surgery, has or will have osteoporosis, kidney disease, neuro-cognitive disorders, cardiovascular disease, gastric problems or	evidence base for surgery is stronger in patients with elevated calcium levels in that we know that surgery lowers calcium levels. Therefore, where we have evidence of a high calcium level, then surgery should be offered. This does not preclude patients with lower calcium levels being considered for surgery.

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				any of the other joys associated with too much calcium running around in the blood for any length of time, creating unpredictable and untold havoc in a patient's organs as it does so. There is no reason whatsoever for this figure to be included in these guidelines.	
Hyperparathyroid UK Action 4 Change	Guideline	5	23 - 24	We are concerned that this main guideline does not detail more symptoms. In order to assist primary care quickly and efficiently to recognise patients presenting with this disease, it would be more beneficial to include a wider range of symptoms reported by patient groups, such as bone and joint pain, nausea, extreme fatigue, forgetfulness and headaches within this main guideline rather than listed in the extensive evidence papers. Some of the symptoms when reported by current patient groups has led to patients being misdiagnosed with fibromyalgia/depression for many years. These guidelines are an opportunity to provide primary care with more specific information relating to presentation of this disease.	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience.
Hyperparathyroid UK Action 4 Change	Guideline	5	23 - 24	Again no mention of toxicity symptoms other than non-specific. Please list the most significant symptoms, most impactful on our lives? Thirst and constipation fade into insignificance compared to the other debilitating symptoms of fatigue, muscle weakness, bone pain, cognitive dysfunction. The recommendations for changes to symptoms on Page 3 should also be applied here, with '*hypercalcemia*' changed to '*primary hyperparathyroidism'*	Thank you for your comment. We have amended the list of symptoms in the committee's discussion of the evidence in evidence report A to reflect those mentioned in your comment on the most common symptoms. In the recommendation we have listed those symptoms commonly associated with hypercalcaemia. We now list the common symptoms based on those provided by you in the section 'terms used in this guideline'.
Hyperparathyroid UK	Guideline	5	26	1.2.1 This should also include high parathyroid	Thank you for your comment. The committee

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Action 4 Change				hormone level with calcium within normal range. People with Normocalcaemic primary hyperparathyroidism have been proven to benefit from surgery. There are many case in our group of people regaining their lives quickly post op. This particular line in this guideline can potentially deny many people the opportunity to regain their lives which is stated as one of your aims and purposes of this guideline on page 1.	discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data on people with calcium below the limits specified. We have expanded the section on hyperparathyroidism in the committee's discussion of the evidence in evidence report B. We have highlighted this topic with the surveillance review team so that any future updates of this guideline will incorporate new evidence when it becomes available.
Hyperparathyroid UK Action 4 Change	Guideline	5	26	1.2.1 At this serum calcium threshold of 2.85, many patients with debilitating symptoms and lower levels will never be cured.	Thank you for your comment. Through the implementation of recommendation 1.3.2 all people with a diagnosis of PHPT will be considered for referral to surgery.
Hyperparathyroid UK Action 4 Change	Guideline	5	26	1.2.1 This weekend's news has included a promise by the NHS of a World Class Service. In order to achieve this for patients with primary hyperparathyroidism, you must recommend surgery based on symptoms, and quality of life, rather than a selective few with calcium of 2.85mmo/l. It has already been established that level of calcium does not dictate the severity of symptoms, and many will either never reach that level of calcium, or will	Thank you for your comment. A calcium level is only specified where it is the only presentation. Through the implementation of recommendation 1.3.2 all people with a diagnosis of PHPT will be considered for referral to surgery.

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				have their lives ruined whilst waiting, so you really ought to remove this restriction and make a point that you are removing it in order to achieve you aim of getting people diagnosed sooner, operated on sooner, getting them back to work and unclogging the doctors and consultants waiting rooms, and A&E departments, of desperately ill people with untreated primary hyperparathyroidism.	
Hyperparathyroid UK Action 4 Change	Guideline	5	26	1.2.1 The inclusion of this >2.85mmol/L criteria is incorrect in every way. Not only does it prevent patients from ensuring they receive the optimum care (the only curative option is surgery) but it also encourages GPs/physicians/surgeons to play-down and somewhat discourage surgery and provide inaccurate information to patients with lower levels of elevated, abnormal serum calcium levels. The distress, anxiety, sickness that has to be endured by many patients due to nonsense such as "your levels have only been between 2.65-2.75, you haven't got kidney disease or osteoporosis yet, so you can't be considered for surgery" is wrong and harmful to the health of patients. Therefore, any mention of serum calcium levels being >2.85mmol/L needs to be removed. There is no numerical level that needs to be included. Excessive amounts of calcium are dangerous to patients. It is not the *height* of calcium that is key, it is the *duration* that higher than normal calcium levels are in	Thank you for your comment. A calcium level is only specified where it is the only presentation. Through the implementation of recommendation 1.3.2 all people with a diagnosis of PHPT will be considered for referral to surgery.

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				the body, whether these be considered towards the lower end of the spectrum or not.	
Hyperparathyroid UK Action 4 Change	Guideline	5	26	1.2.1 We are concerned as to where the level 2.85 has been determined from. Putting a level of 2.85mmol/l on these guidelines in the section that advises refer to surgery "if" may mean that primary care continues to view anything below 2.85 as not suffering with this disease. It may cause confusion and be unclear. Many patients within our current group have experienced symptoms, poor quality of life and suffering with considerably lower levels than 2.85. The repeating of blood test advised against in page 4, line 14, would show that over a period calcium and pth levels do fall and rise and members with calcium that has fallen do still go on to have an adenoma removed during surgery and report health improvements post op.	Thank you for your comment. A calcium level is only specified where it is the only presentation. Through the implementation of recommendation 1.3.2 all people with a diagnosis of PHPT will be considered for referral to surgery.

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Hyperparathyroid UK Action 4 Change	Guideline	5	26	It should be noted that in an assessment of over 10,000 patients with proven PHPT it was found that 85.6% had serum calcium concentrations below 2.875mmol/L and 69% of patients had never had serum calcium concentration above 2.85mmol/L. In addition, 74% of patients in the same study had at least one serum calcium concentration within the normal reference range, "again making the point of the variability seen in patients with PHPT" ("Current Thinking on Parathyroidism", Arrangoiz R, Cordera F (2016)). I therefore reiterate that serum calcium levels are unpredictable, they do not rise as a patient's condition worsens (as the "cut-off" of >2.85mmol/L suggests), they go up and down *unpredictably* due to parathyroid disease, which makes one or more parathyroid glands malfunction. Similarly, Norman et al published a report in January 2017 following the largest study of parathyroid patients to date (20,081 consecutive adults). They assessed *"the symptoms and complications ([kidney stones, osteoporosis, etc) in patients that have a very high calcium and compared them to parathyroid patients with only very mild elevations of calcium The result: NO DIFFERENCE! People with calcium levels of 12.5 (3.125mmol/L) do not have more symptoms, or [kidney] stones, or osteoporosis, or fatigue (or anything) than people with calcium of 10.5 (2.625mmol/L)" It is the* ***duration*** *of calcium levels above 10.0 (2.6mmol/L) in adults over 30 that are associated with complications of hyperparathyroidism"* This is a result that sits with the data NICE has own assessment that there is no evidence to support the dreamt up >2.85mmol/L criteria, not only eradicates the myth that patients/medical professionals need to wait to	Thank you for your comment. In the knowledge and experience of the committee, successful surgery lowers hypercalcaemia. Therefore patients with a calcium level above 2.85 mmol/litre will benefit on the basis that it will reduce their calcium levels. In the absence of evidence the committee decided to make a recommendation consistent with current practice (recommendation 1.3.1). However they recognised that there is a case to be made for people who do not fall into these traditional criteria, and recommended that these patients should be considered for surgery, i.e. surgery should be considered even if none of the symptoms in 1.3.1 are present (recommendation 1.3.2).

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Hyperparathyroid UK Action 4 Change	Guideline	5	26	1.2.1 Quote from "Primary Hyperparathyroidism: Diagnosis, differential diagnosis, and evaluation".- *."Primary hyperparathyroidism — Hypercalcemia in primary hyperparathyroidism is due to parathyroid hormone (PTH)-mediated activation of osteoclasts, leading to increased bone resorption. In addition, intestinal calcium absorption is elevated. Primary hyperparathyroidism is most often due to a parathyroid adenoma. Patients typically have only small elevations in serum calcium concentrations (less than 11 mg/dL or 2.75 mmol/L), and many have mostly high-normal values with intermittent hypercalcemia. Thus, when one suspects primary hyperparathyroidism, as with high-normal serum calcium values in a patient with calcium nephrolithiasis, it may be necessary to obtain a series of serum calcium measurements to detect hypercalcemia".* Why 2.85? The case study of 20,081people from Deva Boon is all about the importance of surgery with PHPTwith not necessarily high levels.	Thank you for your comment. In the knowledge and experience of the committee, successful surgery lowers hypercalcaemia. Therefore patients with a calcium level above 2.85 mmol/litre will benefit on the basis that it will reduce their calcium levels. In the absence of evidence the committee decided to make a recommendation consistent with current practice (recommendation 1.3.1). However they recognised that there is a case to be made for people who do not fall into these traditional criteria, and recommended that these patients should be considered for surgery, i.e. surgery should be considered even if none of the symptoms in 1.3.1 are present (recommendation 1.3.2).
Hyperparathyroid UK Action 4 Change	Guideline	5	26	1.2.1 If this is the approach for hyperparathyroidism will the NICE guidelines for cancer treatment now be recommending that patients must wait until they are stage 2, stage 3 etc. before they can have chemo/radiotherapy. Is this where it's going to end just to save money that in the long run will cause over expenditure?	Thank you for your comment. In the knowledge and experience of the committee, successful surgery lowers hypercalcaemia. Therefore patients with a calcium level above 2.85 mmol/litre will benefit on the basis that it will reduce their calcium levels. In the absence of evidence the committee decided to make a recommendation consistent with current practice (recommendation 1.3.1). However they recognised that there is a case to be made for people who do not fall into these traditional

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					criteria, and recommended that these patients should be considered for surgery, i.e. surgery should be considered even if they do not have the features listed in recommendation 1.3.1 (recommendation 1.3.2).
Hyperparathyroid UK Action 4 Change	Guideline	5	26	I'm a bit confused about the pointers for surgery because it says. 'Symptoms of hypercalcaemia or end organ damage or calcium of 2.85'. It doesn't say 'and; which seems to indicate that you only need one of those things. Is this a misprint? If a patient is only referred with a calcium level over 2.85 hardly anyone would get surgery. It is important that the symptoms of hyperparathyroidism are known and clearly understood.	Thank you for your comment. We did mean 'or' not 'and' as only one of the symptoms needs to be present. We have edited recommendation 1.3.2 to make it clearer that surgery should be considered even if none of the symptoms in 1.3.1 are present.
Hyperparathyroid UK Action 4 Change	Guideline	5	26	1.2.1 Why 2.85 limit specifically? It is my understanding a high calcium and a high PTH but calcium below 2.85 means you will not be referred for surgery but why not when the diagnosis of Primary hyperparathyroidism has to be the balance between calcium and PTH.	Thank you for your comment. In the knowledge and experience of the committee, successful surgery lowers hypercalcaemia. Therefore patients with a calcium level above 2.85 mmol/litre will benefit on the basis that it will reduce their calcium levels. In the absence of evidence the committee decided to make a recommendation consistent with current practice (recommendation 1.3.1). However they recognised that there is a case to be made for people who do not fall into these traditional criteria, and recommended that these patients should be considered for surgery, i.e. surgery should be considered even if they do not have the features listed in recommendation 1.3.1 (recommendation 1.3.2). Some of the symptoms of PHPT are not closely correlated with symptoms of hypercalcaemia. However we do know that surgery lowers calcium levels.

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Hyperparathyroid UK Action 4 Change	Guideline	5	26	1.2.1 2.85 is a ridiculously high calcium level to ensure a surgical referral.	Thank you for your comment. In the knowledge and experience of the committee, successful surgery lowers hypercalcaemia. Therefore patients with a calcium level above 2.85 mmol/litre will benefit on the basis that it will reduce their calcium levels. In the absence of evidence the committee decided to make a recommendation consistent with current practice (recommendation 1.3.1). However they recognised that there is a case to be made for people who do not fall into these traditional criteria, and recommended that these patients should be considered for surgery, i.e. surgery should be considered even if they do not have the features listed in recommendation 1.3.1 (recommendation 1.3.2).
Hyperparathyroid UK Action 4 Change	Guideline	5	26	1.2.1 Never quite understood where the figure of 2.85 mmol/L came from to represent the threshold for treatment, but at least 1.2.2 allows for referral for surgery to be considered, irrespective of classic symptoms or level of hypercalcaemia, so in fact anyone with a diagnosis of HPT could be considered for surgery.	Thank you for your comment. In the knowledge and experience of the committee, successful surgery lowers hypercalcaemia. Therefore patients with a calcium level above 2.85 mmol/litre will benefit on the basis that it will reduce their calcium levels. In the absence of evidence the committee decided to make a recommendation consistent with current practice (recommendation 1.3.1). However they recognised that there is a case to be made for people who do not fall into these traditional criteria, and recommended that these patients should be considered for surgery, i.e. surgery should be considered even if they do not have the features listed in recommendation 1.3.1 (recommendation 1.3.2).
Hyperparathyroid UK Action 4 Change	Guideline	5	26	1.2.1 There is no point having new guidelines if the committee are using outdated papers and outdated practices to continue the same old ways. We campaigned for these guidelines	Thank you for your comment. All of the relevant literature was searched up to 6 August 2018. The committee acknowledges that some of the evidence was of low quality/outdated, and in these instances

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				because change is needed. There are surgeons in the UK who don't accept that only patients with calcium over 2.85mmol/l qualify for surgery. What patients need is guidelines to recommend that all surgeons, doctors and endocrinologists are made aware this is outdated practice that needs to be abolished.	took this into account when making recommendations. Where evidence was low quality, the committee also considered factors such as current practice, and clinical experience.
Hyperparathyroid UK Action 4 Change	Guideline	5	26	1.2.1 The conditions here for referring patients for surgery take no account of patients with normocalcaemic and normohormonal hyperparathyroidism.	Thank you for your comment. The committee's definition of PHPT that is used in the guideline does not preclude people with normal calcium or with mid-range PTH being diagnosed with PHPT. In the knowledge and experience of the committee, successful surgery lowers hypercalcaemia. Therefore patients with a calcium level above 2.85 mmol/litre will benefit on the basis that it will reduce their calcium levels. In the absence of evidence the committee decided to make a recommendation consistent with current practice (recommendation 1.3.1). However they recognised that there is a case to be made for people who do not fall into these traditional criteria, and recommended that these patients should be considered for surgery, i.e. surgery should be considered even if none of the symptoms in 1.3.1 are present (recommendation 1.3.2).
Hyperparathyroid UK Action 4 Change	Guideline	5	26	1.2.1 To refer to a surgeon only those patients with calcium over 2.85 is to exclude and deny surgery to the majority of patients with primary hyperparathyroidism. This level must be removed from this guideline. You have already stated correctly that the only cure is surgery. If this has somehow been determined as a cost saving parameter, it is in fact a seriously false and misguided inclusion as primary	Thank you for your comment. In the knowledge and experience of the committee, successful surgery lowers hypercalcaemia. Therefore patients with a calcium level above 2.85 mmol/litre will benefit on the basis that it will reduce their calcium levels. In the absence of evidence the committee decided to make a recommendation consistent with current practice (recommendation 1.3.1).

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				hyperparathyroidism is without doubt a progressive disease that will undoubtedly cost the NHS more long term, per person to manage untreated, than a parathyroidectomy. I would suggest instead that a referral to surgeon should be determined based on criteria such as the quality of life, range of symptoms and length of time the patient has suffered from primary hyperparathyroidism.	However they recognised that there is a case to be made for people who do not fall into these traditional criteria, and recommended that these patients should be considered for surgery, i.e. surgery should be considered even if they do not have the features listed in recommendation 1.3.1 (recommendation 1.3.2).
Hyperparathyroid UK Action 4 Change	Guideline	5	26	I strongly recommend that the level 2.85 as a recommendation for surgery is removed from this guideline	Thank you for your comment. In the knowledge and experience of the committee, successful surgery lowers hypercalcaemia. Therefore patients with a calcium level above 2.85 mmol/litre will benefit on the basis that it will reduce their calcium levels. In the absence of evidence the committee decided to make a recommendation consistent with current practice (recommendation 1.3.1). However they recognised that there is a case to be made for people who do not fall into these traditional criteria, and recommended that these patients should be considered for surgery, i.e. surgery should be considered even if they do not have the features listed in recommendation 1.3.1 (recommendation 1.3.2).
Hyperparathyroid UK Action 4 Change	Guideline	5	26	2.85 is extremely high, damage is being done to the body at levels considerably lower than that.	Thank you for your comment. In the knowledge and experience of the committee, successful surgery lowers hypercalcaemia. Therefore patients with a calcium level above 2.85 mmol/litre will benefit on the basis that it will reduce their calcium levels. In the absence of evidence the committee decided to make a recommendation consistent with current practice (recommendation 1.3.1). However they recognised that there is a case to be

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					made for people who do not fall into these traditional criteria, and recommended that these patients should be considered for surgery, i.e. surgery should be considered even if they do not have the features listed in recommendation 1.3.1 (recommendation 1.3.2).
Hyperparathyroid UK Action 4 Change	Guideline	5	26	As you have already stated in this guideline, calcium levels can fluctuate. Are you aware that this restrictive number may not be 'caught' by a blood test on someone whose levels are fluctuating and you are in fact recommending a numbers lottery? A blood test is a moment in time.	Thank you for your comment. The committee recognises that there is some fluctuation in serum calcium (and also in the precision of the assays), and this is why we are recommending repeated tests.
Hyperparathyroid UK Action 4 Change	Guideline	5	26	1.2.1 If a patient has a diagnosis of primary hyperparathyroidism, waiting to operate on them until they have an albumin-adjusted serum calcium level of 2.85 mmol/litre or above is dangerous. They are at risk of DVTs, stroke, or heart attack.	Thank you for your comment. In the knowledge and experience of the committee, successful surgery lowers hypercalcaemia. Therefore patients with a calcium level above 2.85 mmol/litre will benefit on the basis that it will reduce their calcium levels. In the absence of evidence the committee decided to make a recommendation consistent with current practice (recommendation 1.3.1). However they recognised that there is a case to be made for people who do not fall into these traditional criteria, and recommended that these patients should be considered for surgery, i.e. surgery should be considered even if none of the symptoms in 1.3.1 are present (recommendation 1.3.2).
Hyperparathyroid UK Action 4 Change	Guideline	6	1 - 3	It makes more sense to write these lines before rather than after 1-2.1, especially as the majority of our members fit into this non specified criteria.	Thank you for your comment. The committee considered re-ordering the recommendations but the recommendation where there is clearer evidence of benefit was presented first.
Hyperparathyroid UK Action 4 Change	Guideline	6	1 - 3	1.2.2 Lines1- 3 contradict the recommendation 1.2.1 on Page 5. Why would you make a recommendation for referral for surgery with	Thank you for your comment. The committee was satisfied on the basis of the evidence that surgery is indicated for those in whom it is currently being

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				restrictive levels only to contradict it in the following recommendation? Considering all the comments in dispute of 1.2.1, we recommend they be condensed into one recommendation which should read: Refer people with primary hyperparathyroidism to a surgeon with expertise in parathyroid surgery. It will help the surgeon to prioritise surgical lists by including the following information: • symptoms of primary hyperparathyroidism • biochemical history of hypercalcemia or inappropriate calcium and PTH relationship if calcium is not elevated above the population reference range (including magnesium & vitamin D level if appropriate), • end-organ disease (renal stones, fragility fractures or osteoporosis)	performed, and for this group made an 'offer' recommendation (1.3.1). However they recognised that there is a case to be made for people who do not fall into these traditional criteria, and recommended these patients should be considered for surgery (recommendation 1.3.2).
Hyperparathyroid UK Action 4 Change	Guideline	6	1 - 3	1.2.2 Referral to a surgeon with expertise in parathyroid surgery should be undertaken irrespective of the features in 1.2.1 as the range of symptoms and biochemical presentations of this disease is vast. Each sufferer presents differently. I believe this sentence ought to be mentioned in 1.2.1 also or referenced in 1.2.1 to avoid the possibility of confusion leading to a missed referral.	Thank you for your comment. The committee agreed. We have now edited recommendation 1.3.2 to make it clearer.
Hyperparathyroid UK Action 4 Change	Guideline	6	7 - 8	1.3.1 We are in complete agreement and very relieved to see this.	Thank you for your comment
Hyperparathyroid UK Action 4 Change	Guideline	6	7 - 8	1.3.1 This sentence is so important. Please will you find a way to get this very important message across to doctors and	Thank you for your comment. We have made the NICE implementation team aware of this comment.

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				endocrinologists? We hear so many times that delays are the result of negative scans. It would be far better for the patient to be referred to a surgeon with expertise by the surgeon or endocrinologist who feels that a negative scan, despite obviously positive biochemical results, means the patient is put on a 'watch and wait' list. Increased awareness at endocrine level is vitally important regarding negative scans as we are aware of a large number of patients who are denied a referral to surgery on the basis of their negative scan, and remain clogged in the system, suffering needlessly.	
Hyperparathyroid UK Action 4 Change	Guideline	6	7 - 8	1.3.1 Fully endorse this. This is not done universally throughout the UK. It would avoid needless delays prior to an operation.	Thank you for your comment.
Hyperparathyroid UK Action 4 Change	Guideline	6	9 - 10	1.3.2 Primary care can only request an ultrasound scan. This has been confirmed by my GP this week.	Thank you for your comment. Pre-operative imaging including ultrasound is performed in secondary care in those who have met the criteria for surgery.
Hyperparathyroid UK Action 4 Change	Guideline	6	9 - 10	1.3.2 Pre-operative imaging in terms of ultrasound and Sestamibi scans, can and does give rise to negative results in a large number of cases. This is a well-known fact. Most ultrasound scans are performed by general radiologists who don't always have the skill or expertise required to find parathyroid glands, adenomas or glands with hyperplasia. It would be beneficial if these scans can be performed by a radiologist who is experienced in finding parathyroid glands, or alternatively recommend all radiologists should be trained/prepared to look for parathyroid glands.	Thank you for your comment. The committee recognise that training is an important issue but unfortunately this topic was not prioritised during the scoping process for this guideline.
Hyperparathyroid UK	Guideline	6	9 - 10	1.3.2 Ultrasound is very unreliable in non-	Thank you for your comment. We refer to the

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Action 4 Change				expert hands.	availability of expertise for ultrasound scanning. Sestamibi can be performed if this expertise is not available.
Hyperparathyroid UK Action 4 Change	Guideline	6	11 - 12	1.3.3 Sestamibi scans do not always show adenomas accurately, especially in some hospitals with older equipment. If a patient has been diagnosed with PHPT but their ultrasound/Sestamibi scans are negative, efforts should be made to locate the adenoma/enlarged glands using alternative scanning modalities; 4D CT scans and Choline Pet scans especially after a failed parathyroidectomy in cases of suspected ectopic glands to reduce the incidence of further failed re-operations	Thank you for your comment. The committee recommended that if the first imaging modality is negative then there is no requirement to scan with a second imaging test, and proceeding straight to 4-gland exploration will avoid any unnecessary radiation for the person. The committee agreed that in a situation of positive first imaging modality but negative second modality scan, a third scan would be unlikely to add anything and the preferred approach would be to proceed to 4-gland exploration. The committee agreed that in situations where dual scanning fails to identify an adenoma or are discordant, further imaging should not be offered as it will not add useful information and will expose the person to unnecessary radiation, and these cases should proceed to surgery.
Hyperparathyroid UK Action 4 Change	Guideline	6	13 - 14	1.3.4 There should be a recommendation here about surgeons finding glands in unusual locations such as the carotid sheath, near the spine and thymus, which can be a reason for negative scans and therefore let the surgeon choose to request further scans.	Thank you for your comment. Recommendation 1.4.4 does recommend surgery for people with negative localisation. If the 4-gland exploration is not successful we recommend a multidisciplinary team review (recommendation 1.4.13). This review may lead to additional imaging.
Hyperparathyroid UK Action 4 Change	Guideline	6	13 - 14	1.3.4 We are concerned with the recommendation to not offer more imaging whilst we do completely agree negative scans should not prevent a referral to a surgeon, we are aware that a note of caution should be included here regarding the possibility of ectopic adenomas and the likelihood a surgeon may have to look for ectopic glands within the thyroid, the thymus, the carotid sheath, the clavicle or near the chest wall. A	Thank you for your comment. If the 4-gland exploration is not successful we recommend a multidisciplinary team review (recommendation 1.4.13). This review may lead to additional imaging. The surgeon should have expertise in reoperative parathyroid surgery.

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				surgeon who has not performed such explorations may feel more inclined to request a CT with contrast scan, or refer to a more experienced surgeon. On many occasions within our organisation we have seen ectopic glands found on a CT with contrast scan, which has either saved a failed operation due to a missed gland and a further need for re-op, or has been found after failed surgery and would have saved the need for re-op if it had been done pre surgery.	
Hyperparathyroid UK Action 4 Change	Guideline	6	15 - 16	1.3.5 This reinforces the commentwe submitted for 1.3.4	Thank you for your comment. We have answered your comment for 1.4.4.
Hyperparathyroid UK Action 4 Change	Guideline	6	15 - 16	1.3.5 Only skilled and experienced parathyroid surgeons should be given responsibility for four gland assessment surgery to minimise any potential damage to vocal chords, thyroid glands and normal parathyroid glands. A less experienced surgeon looking to find an adenoma or enlarged gland(s) as a matter of routine after negative scans should not be advocated until all measures have been exhausted to locate them. Re-operations come with greater risk due to scar tissue.	Thank you for your comment. The committee agreed, and the committee has referred to a centre with relevant expertise in the recommendation.
Hyperparathyroid UK Action 4 Change	Guideline	6	15 - 16	1.3.5 We absolutely agree. We have a growing list of approved surgeons and are also aware of some surgeons who have failed to find an ectopic gland the first time and have shown determination to find it the second time, performed successive sestamibi or CT contrast scans and succeeded to locate the gland the second time. We are convinced those surgeons will have learned from the experience and have faith in recommending them.	Thank you for your comment.

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Hyperparathyroid UK Action 4 Change	Guideline	6	15 - 16	1.3.5 It is impossible to identify centres with relevant expertise by looking at the BAETS audits at the moment. We highly recommend a surgeon who is not on the list. From experience we know which surgeons are aware of normocalcemic primary hyperparathyroidism and which centres are not. It is important for GP practices and also endocrinologists to become more aware of their local surgeons practices with regards to surgery. We find endocrinologists often have a contradicting opinion to the surgeon they refer to, which is less than helpful and can be stressful for the patient when they have to take alternative steps to bypass the endocrinologist to get the referral they need. This is not acceptable. It should not be this way.	Thank you for your comment. The committee acknowledged the importance of the experience of the surgeon but NICE guidelines are not able to recommend specific surgeons or centres.
Hyperparathyroid UK Action 4 Change	Guideline	6	15 - 16	1.3.5 Primary care has already been highlighted to have a lack of awareness and information available regarding this disease. Please use these guidelines as an opportunity to provide detailed advice for primary care. In terms of equality, we do not necessarily consider specialist centres to be those with the highest audit figures alone, not all centres throughout the country follow the same procedures, or are easily accessible by all patients in terms of work, travel, families, affordability. This can all cause further stress and worry whilst already feeling unwell with this disease. What you may consider a specialist centre may not be a recommended specialist centre to us. It is very important to highlight the need for	Thank you for your comment. The recommendations provide clear guidance to people in primary care regarding albumin-adjusted serum calcium and PTH testing and also when to seek advice from a specialist. The NICE implementation team will support the implementation of these recommendations. The committee acknowledged the importance of the experience of the surgeon but NICE guidelines are not able to recommend specific surgeons or centres.

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				frank discussions between patients, primary care, endocrine consultants and their chosen surgeon so the patient feels in safe hands and reassured their journey to surgery will be handled with care and respect, with all consultants singing from the same hymn sheet in order to avoid unnecessary delays, uncertainty and worsening quality of life. Audits for parathyroid surgery should not be limited to number of surgeries performed, but should include information based on honest success rates. We would like to see who has experience of finding ectopic glands, how many are found first time. Pictures of incision sites, details of post-operative advice and care. Specialist centres to our members are the centres who provide all this and do not leave their patients desperately calling out for help to a support group in the middle of the night after discharge from hospital. Currently our members get all this information from us, but we are concerned for those people who don't know about us and don't yet have access to this information which should be available to all.	
Hyperparathyroid UK Action 4 Change	Guideline	6	18	1.3.6 Four gland exploration should be standard as it is more cost effective in the long term if it saves the patient the stress of re diagnosis and going through a re-op.	Thank you for your comment. The committee, based on their experience and evidence, agreed that people should be offered a choice of focused parathyroidectomy or 4-gland exploration if the preoperative imaging shows a single adenoma in the neck. The committee agreed on the basis of their clinical experience that for people whose pre-operative imaging (first modality scan with or without a second modality scan) is negative or does not identify a single adenoma, 4-gland exploration should be offered. The

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					committee discussed that in patients with negative imaging, 4-gland exploration is the optimal management because of the increased frequency of multi-glandular disease in such cases.
Hyperparathyroid UK Action 4 Change	Guideline	6	18 - 20	1.3.6 I find this sentence substantially lacking substance and detail. It reminds me of when I order a bacon sandwich and I'm offered 'white or brown bread'? It really should say: Explain to the patient the pros and cons of both a focused parathyroidectomy and a 4 gland exploration. The decision should be a mutual agreement based on; the understanding pre-operative imaging is not always conclusive, whether or not intraoperative pth testing is used, the possibility of a gland not being located in the position on the scan, or even found in an expected position, the reality that a focused parathyroidectomy could evolve into an exploration due to an ectopic gland and a detailed treatment plan should a focused parathyroidectomy be chosen and not be successful for any of the previous reasons.	Thank you for your comment. We have added that benefits and risks should be discussed to recommendation 1.4.6 and the areas on which information should be given.
Hyperparathyroid UK Action 4 Change	Guideline	7	2 - 3	1.3.9 If intraoperative parathyroid hormone testing is available, what is the rationale for not using it during first time surgery? If it can assist surgeons with confirming levels of pth have fallen correctly?	Thank you for your comment. The committee considered that there was not sufficient evidence to recommend IOPTH for first-time surgery. The committee from their knowledge and experience stated that there was a marginal benefit (0.9%-1.4%) with the use of IOPTH but debated if this was significant. They also noted that this marginal benefit could be partially attributed to surgical expertise. An exploratory cost effectiveness threshold analysis was undertaken for the use of IOPTH, which suggested that due to the high cost of testing and the very small marginal gain of using IOPTH as a result of the already high rates of successful surgery, IOPTH is

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					highly unlikely to be cost effective at the NICE £20,000 per QALY gained threshold.
Hyperparathyroid UK Action 4 Change	Guideline	7	2 - 3	1.3.9 Why not? Is intraoperative assay not cost effective? I understand not all boards have technology to offer this but should this be gold standard?	Thank you for your comment. The committee considered that there was not sufficient evidence to recommend IOPTH for first-time surgery. The committee from their knowledge and experience stated that there was a marginal benefit (0.9%-1.4%) with the use of IOPTH but debated if this was significant. They also noted that this marginal benefit could be partially attributed to surgical expertise. An exploratory cost effectiveness threshold analysis was undertaken for the use of IOPTH, which suggested that due to the high cost of testing and the very small marginal gain of using IOPTH as a result of the already high rates of successful surgery, IOPTH is highly unlikely to be cost effective at the NICE £20,000 per QALY gained threshold.
Hyperparathyroid UK Action 4 Change	Guideline	7	2 - 3	1.3.9 I think it is much too dogmatic and inflexible to make this recommendation. The reasons why it is made are extremely complex and I don't doubt that much thought has gone into this whole matter, but I am not convinced that Guys/St Thomas' and the Hammersmith will abandon use of IOPTH when they have access to the equipment and where they see fit to use it. Once again, I feel that this should be couched in the terms of a recommendation rather than an outright proscription.	Thank you for your comment. The recommendations made are guidelines and if centres that already have this equipment consider that they have a strong case to use IOPTH testing in certain cases then they may do so. The committee considered that there was not sufficient evidence to recommend IOPTH for first-time surgery. The committee from their knowledge and experience stated that there was a marginal benefit (0.9%-1.4%) with the use of IOPTH but debated if this was significant. They also noted that this marginal benefit could be partially attributed to surgical expertise. Using more favourable estimates of benefit of IOPTH, an exploratory economic analysis was undertaken, which suggested that IOPTH is highly unlikely to be cost effective due to the high cost of IOPTH testing and the small percentage increase in successful parathyroidectomies. This economic analysis also

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					considered a scenario where the testing machine required for IOPTH was £0, suggestive of a scenario of centres that currently have the machine for testing. This analysis still found that IOPTH was highly unlikely to be cost effective as the cost of the reagents required to undertake IOPTH testing is high. Therefore, the committee considered that IOPTH should not be recommended in first-time parathyroid surgery. There was no clinical evidence on the use of IOPTH in repeat surgery and therefore the committee did not make a recommendation for this.
Hyperparathyroid UK Action 4 Change	Guideline	7	2 - 3	1.3.9 I don't entirely agree with that. Relying purely on a standard concordant MIBI+USS, targeted parathyroidectomy runs a risk of missing the second adenoma/asymmetric hyperplasia, and failure rate is reduced with iopth. I know that the actual magnitude of this reduction is very small, however, and I suspect that is the reasoning behind this recommendation. I also consider iopth an essential for re-operative surgery, where risks are all higher.	Thank you for your comment. The committee considered that there was not sufficient evidence to recommend IOPTH for first-time surgery. The committee from their knowledge and experience stated that there was a marginal benefit (0.9%-1.4%) with the use of IOPTH but debated if this was significant. They also noted that this marginal benefit could be partially attributed to surgical expertise.
Hyperparathyroid UK Action 4 Change	Guideline	7	2 - 3	1.3.9 The avoidance of intra-operative monitoring of PTH for first time parathyroid surgery has been justified on the basis of cost alone. This is not a logical decision. I believe it offers both the surgeon and the patient comfort the surgery has been undertaken properly and thoroughly. I appreciate it is not fool proof because PTH can decrease after the removal of an adenoma but increase again post-surgery if the patient has more than one adenoma or has enlarged glands, but using intra-operative monitoring together with 4-gland assessment should not be completely	Thank you for your comment. This recommendation was made in consideration of both clinical and cost effectiveness. The committee discussed that the clinical effectiveness of IOPTH in first operation for parathyroidectomy is mixed and highly uncertain. The committee considered that there was not sufficient evidence to recommend IOPTH for first-time surgery. The committee from their knowledge and experience stated that there was a marginal benefit (0.9%-1.4%) with the use of IOPTH but debated if this was significant. They also noted that this marginal benefit could be partially attributed to surgical expertise.

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				ruled out. Surely it is imperative to do everything possible to ensure the surgery is a success the first time round rather than cutting corners for the sake of cost and having to undertake a re-operation because the surgery failed the first time. Why should a patient be denied this right to care? Cancer patients aren't denied access to cool cap treatment even though a large percentage of them lose their hair anyway (I speak from experience) so why should a hyperparathyroid patient be denied a tool that will improve the chances of their surgery being a success?	Taking this into consideration, an economic evaluation was undertaken using this more favourable effectiveness data and taking into account the need for reoperation due to failed surgery. This analysis found that IOPTH was highly unlikely to be cost effective due to the high cost of the test as well as the very small gain in successful parathyroidectomies as a result of using IOPTH. Therefore the committee made a recommendation that IOPTH should not currently be used in first operations for parathyroidectomy.
Hyperparathyroid UK Action 4 Change	Guideline	7	2 - 3	1.3.9 Intraoperative parathyroid hormone monitoring should be used in first time surgery as this may prevent missing a 2nd adenoma. We have seen this happen within our group too many times to dismiss it.	Thank you for your comment. There was limited evidence on intraoperative parathyroid hormone (IOPTH) monitoring. The committee noted that in their experience there is a marginal benefit with the use of IOPTH, but this could be partially attributed to surgical expertise. IOPTH monitoring is costly and its effectiveness in improving surgical outcomes is uncertain. An economic evaluation was undertaken using more favourable effectiveness data and taking into account the need for reoperation due to unsuccessful surgery. This analysis found that IOPTH was highly unlikely to be cost effective due to the high cost of the test as well as the very small gain in successful parathyroidectomies as a result of using IOPTH. Therefore the committee agreed that their experience together with the limited evidence did not support IOPTH monitoring as part of standard practice.
Hyperparathyroid UK Action 4 Change	Guideline	7	2 - 3	1.3.9 If only one side is explored an adenoma on the other side could be missed, testing intraoperatively would reduce the number of	Thank you for your comment. There was limited evidence on intraoperative parathyroid hormone (IOPTH) monitoring. The committee noted that in their

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				adenomas missed and the need for the trauma of further tests and a re-op costs.	experience there is a marginal benefit with the use of IOPTH, but this could be partially attributed to surgical expertise. IOPTH monitoring is costly and its effectiveness in improving surgical outcomes is uncertain. An economic evaluation was undertaken using more favourable effectiveness data and taking into account the need for reoperation due to unsuccessful surgery. This analysis found that IOPTH was highly unlikely to be cost effective due to the high cost of the test as well as the very small gain in successful parathyroidectomies as a result of using IOPTH. Therefore the committee agreed that their experience together with the limited evidence did not support IOPTH monitoring as part of standard practice.
Hyperparathyroid UK Action 4 Change	Guideline	7	2 - 3	1.3.9 Intraoperative parathyroid hormone monitoring should be used in first time surgery as this may prevent missing a second adenoma. It should be noted that there are a significant number of failed surgeries due to multigland disease. This may be avoided if IOPHT is carried out.	Thank you for your comment. There was limited evidence on intraoperative parathyroid hormone (IOPTH) monitoring. The committee noted that in their experience there is a marginal benefit with the use of IOPTH, but this could be partially attributed to surgical expertise. IOPTH monitoring is costly and its effectiveness in improving surgical outcomes is uncertain. An economic evaluation was undertaken using more favourable effectiveness data and taking into account the need for reoperation due to unsuccessful surgery. This analysis found that IOPTH was highly unlikely to be cost effective due to the high cost of the test as well as the very small gain in successful parathyroidectomies as a result of using IOPTH. Therefore the committee agreed that their experience together with the limited evidence did not support IOPTH monitoring as part of standard practice.
Hyperparathyroid UK Action 4 Change	Guideline	7	2 - 3	1.3.9 As this is obviously a recommendation to surgeons only, I think it has to be a	Thank you for your comment. There was limited evidence on intraoperative parathyroid hormone

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				consideration weighed up by the surgeon based on his own experience rather than a 'Do not use intraoperative parathyroid hormone monitoring in first-time parathyroid surgery. The evidence admitted in these guidelines proves there is a lack of UK research to date and the cost alone of an intraoperative PTH test bears no comparison on a reop, yet	(IOPTH) monitoring. The committee noted that in their experience there is a marginal benefit with the use of IOPTH, but this could be partially attributed to surgical expertise. IOPTH monitoring is costly and its effectiveness in improving surgical outcomes is uncertain. An economic evaluation was undertaken using more favourable effectiveness data and taking into account the need for reoperation due to unsuccessful surgery. This analysis found that IOPTH was highly unlikely to be cost effective due to the high cost of the test as well as the very small gain in successful parathyroidectomies as a result of using IOPTH. Therefore the committee agreed that their experience together with the limited evidence did not support IOPTH monitoring as part of standard practice.
Hyperparathyroid UK Action 4 Change	Guideline	7	2 - 3	1.3.9 Has Professor Jon Wass been consulted for his opinion in his role as clinical lead for Endocrinology at Getting it Right First Time? (GIRFT). http://gettingitrightfirsttime.co.uk/medical-specialties/endocrinology/	Thank you for your comment. Individuals are able to comment through their organisations if they are registered as stakeholders.
Hyperparathyroid UK Action 4 Change	Guideline	7	2 - 3	1.3.9 There are a number of members in our organisation needing re-ops who wish they had been offered intraoperative parathyroid hormone testing during their failed parathyroidectomy.	Thank you for your comment.
Hyperparathyroid UK Action 4 Change	Guideline	7	2 - 3	1.3.9 The use of intraoperative PTH monitoring can help prevent failed surgeries resulting in additional costs and add to the suffering of the patient.	Thank you for your comment. There was limited evidence on intraoperative parathyroid hormone (IOPTH) monitoring. The committee noted that in their experience there is a marginal benefit with the use of IOPTH, but this could be partially attributed to surgical expertise. This was discussed by the committee and taken into consideration in the exploratory economic analysis

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					undertaken, which found that IOPTH is highly unlikely to be cost effective. The committee agreed that their experience together with the limited evidence did not support IOPTH monitoring as part of standard practice.
Hyperparathyroid UK Action 4 Change	Guideline	7	2 - 3	1.3.9 If intraoperative PTH monitoring is not offered at first surgery, regardless of if adenoma and / or hyperplasia is found, surgeon cannot be sure that outcome will be successful and risks multiple surgeries rather than 'right first time' which risks wasting NHS money and resources as well as being detrimental to the patient.	Thank you for your comment. There was limited evidence on intraoperative parathyroid hormone (IOPTH) monitoring. The committee noted that in their experience there is a marginal benefit with the use of IOPTH, but this could be partially attributed to surgical expertise. IOPTH monitoring is costly and its effectiveness in improving surgical outcomes is uncertain. The need for repeat surgery was taken into consideration in the exploratory economic analysis undertaken, which found that IOPTH is highly unlikely to be cost effective. The committee agreed that their experience together with the limited evidence did not support IOPTH monitoring as part of standard practice.
Hyperparathyroid UK Action 4 Change	Guideline	7	2 - 3	1.3.9 Intraoperative parathyroid hormone monitoring should be used in first time parathyroid surgery as a fall in PTH by more than 50% is a good indicator of a successful surgical removal of the parathyroid adenoma and would decrease the likelihood of the patient having to undergo a further operation to remove a second, or more, adenoma(s).	Thank you for your comment. There was limited evidence on intraoperative parathyroid hormone (IOPTH) monitoring. The committee noted that in their experience there is a marginal benefit with the use of IOPTH, but this could be partially attributed to surgical expertise. IOPTH monitoring is costly and its effectiveness in improving surgical outcomes is uncertain. The need for repeat surgery was taken into consideration in the exploratory economic analysis undertaken, which found that IOPTH is highly unlikely to be cost effective. The committee agreed that their experience together with the limited evidence did not support IOPTH monitoring as part of standard practice.
Hyperparathyroid UK Action 4 Change	Guideline	7	2 - 3	The British Association of Endocrine and Thyroid Surgeons Fifth National Audit 2017 mentions Intra operative PTH assay in	Thank you for your comment. The committee was aware of the data from the Fifth National audit report by The British Association of Endocrine & Thyroid

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				'Outcomes – Persisting Hypercalcaemia': *'Use of intra-operative PTH assay significantly improves the cure rate, although the absolute improvement is relatively small. This, along with the added expense and time taken to perform qPTH during surgery may explain why it has not been more uniformly adopted'.* They include a table' Glands removed and age at operation' which lists a total of 1,324 people in total with 2 glands removed, the highest numbers of 391 and 309 people were between the ages of 61-70 and 71-80 respectively and 270 at ages 51-60. Maybe these audits ought to be considered and a recommendation for intra operative PTH assay recommended accordingly. The following article is from Endocrinology adviser January 2019: 'Intraoperative Monitoring of PTH May Simplify Surgical Care for Primary Hyperparathyroidism https://www.endocrinologyadvisor.com/thyroid/parathyroid-hormone-monitoring-during-parathyroidectomy-improves-cure-rate/article/824284/ *'Ultrasound and MIBI scans were measured for sensitivity, specificity, accuracy, and other factors and cases of intraoperative PTH monitoring were assessed for added value, defined as the percentage of patients in whom the monitoring significantly influenced the course of operation or contributed to achieving*	Surgeons and took this into consideration when making the recommendations. The evidence for IOPTH was sought from both test-and-treat RCT studies and from diagnostic accuracy studies. The study was not included as the paper was after the cut-off, but due to the robustness of the economic model it would not change the recommendation.

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				a cure. A cure was defined as albumin-adjusted calcium ≤2.6 mmol/L during follow-up. *A total of 603 included patients were successfully cured (97.7%). Intraoperative PTH monitoring was found to have a sensitivity rate of 98.6% (P <.05) compared with 78.2% for ultrasound and 70% for MIBI (P <.05). In a similar fashion, intraoperative PTH monitoring had a sensitivity of 98.8% in detecting single-gland disease and 96.7% for multigland disease, while ultrasound and MIBI were less sensitive for both (85% vs 55% and 77.5% vs 45.5% for single- vs multigland disease, respectively; P <.05 for all).* *In 41 cases in which ultrasound provided inaccurate predictions, MIBI correctly diagnosed 12 patients (29.3%) while intraoperative PTH monitoring accurately predicted cure in 41 (97.6%).* *Furthermore, intraoperative PTH monitoring offered significant added value in the whole cohort (14%), as well as in patient subgroups with concordant vs discordant scans, minimally invasive vs conventional surgery, and initial vs re-operative surgery (P <.05).* *The researchers noted a lack of a control group as one limitation of their study.*	
Hyperparathyroid UK Action 4 Change	Guideline	7	5 - 6	This recommendation should explain why serum calcium should also be measured before discharge after surgery for primary hyperparathyroidism. Calcium and PTH levels should be recorded on the discharge sheet,	Thank you for your comment. We have added a sentence to the committee's discussion of the evidence to evidence report K on making people aware of what signs and symptoms to watch out for following surgery. Recommendation 1.8.5 specifies that the

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				should the patient experience symptoms of pins and needles around the hands and/or feet and face, it is very important for the patient to understand their calcium is low and how to either treat it or seek medical assistance knowing their levels at discharge from hospital. Should their pins and needles start to turn to cramp it is vital they get medical assistance quickly. Knowing their levels can save time in an emergency should they be experiencing tetany.	clinician should discuss ongoing care and monitoring for primary hyperparathyroidism, explaining the type and frequency of monitoring that will be offered and the purpose of each.
Hyperparathyroid UK Action 4 Change	Guideline	7	5 - 6	It is essential to include a recommendation for post op supplements of calcium if needed, based on symptoms of hypocalcemia such as tingling fingers and mouth. Vitamin D and magnesium are also essential to regain bone strength as well as to benefit from supplemental vitamin D and calcium. To recommend or prescribe either without magnesium is irresponsible. We had to advise a member recently; in hospital with low calcium and PTH post op, to have magnesium tested. She was found to have hypomagnesemia and consequently IV magnesium was implemented. It is astonishing that members are having to ask us because their consultants don't know this. Without correcting the hypomagnesemia, she would have been unable to increase calcium or PTH. This is a vital inclusion for post op care. There is a mention of magnesium further on but it needs to be here also because of its importance.	Thank you for your comment. Post-operative supplementation was not prioritised during the scoping process of this guideline. The committee has highlighted the importance of measuring vitamin D and correcting any deficiency in treating patients with primary hyperparathyroidism. Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function. This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects on PTH secretion or function in PHPT. We have added this to the committee's discussion of the evidence.
Hyperparathyroid UK Action 4 Change	Guideline	7	5 - 6	There should be a recommendation both here and in Table 1 regarding post op supplementation with calcium, vit D,	Thank you for your comment. Post-operative supplementation was not prioritised during the scoping process of this guideline.

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				magnesium and boron. I had no guidance at all about immediate or long-term post-op care and supplements.	
Hyperparathyroid UK Action 4 Change	Guideline	7	5 - 6	Please note this guideline from Oxford University Hospitalsl regarding hypomagnesemia. Hypercalcemia is listed as a cause for hypomagnesemia. From experience and knowledge about the importance of magnesium for bone strength, and also when supplementing with vitamin D and/or calcium, we feel it is essential for this guideline to also be aware and make those who read it aware of the importance of magnesium in relation to primary hyperparathyroidism. http://nssg.oxford-haematology.org.uk/oxford/clinical-care/H-95-guidelines-for-management-of-hypomagnesaemia-in-adult-clinical-haematology.pdf	Thank you for your comment. Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function. This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/ hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects on PTH secretion or function in PHPT. We have added this to the committee's discussion of the evidence.
Hyperparathyroid UK Action 4 Change	Guideline	7	5 - 6	We believe it is essential to include testing of RBS Magnesium here also. We often have calls for help from members who are left in position of low calcium and PTH post op. We understand low magnesium is a contributory cause. Recently a member still in hospital on her second day post-surgery contacted us for help with low calcium and PTH. We advised her to ask for magnesium blood test. Hypomagnesemia was found and IV magnesium administered. We recommend research should be conducted with some urgency on the effect of magnesium on parathyroid hormone in humans. Please read this bovine study: https://link.springer.com/article/10.1007%2FBF	Thank you for your comment. Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function. This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects on PTH secretion or function in PHPT. We have added this to the committee's discussion of the evidence.

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				02408542 Extract: *In a well-defined in vitro perfusion system, the effects of extracellular magnesium concentration (Mg) on parathyroid hormone (PTH) secretion by bovine parathyroid tissue were examined. At Mg less than 0.8 mM, the ability of the glands to secrete hormone maximally in response to low calcium (Ca) stimulation was progressively impaired. Low Mg also impaired the ability of isoproterenol, dibutyryl cyclic AMP and theophylline to stimulate hormone release. The defect in hormone release at low Mg observed in vitro was analogous to the well-documented inhibition of secretion observed in vivo. Increases in Mg from 0 to 0.8 mM rapidly repaired the defect in hormone secretion. At Mg above 1.0 mM there was a Ca-like effect on hormone release, with a progressive decrease in secretion at increased Mg. Although its mechanism is not yet clear, the low Mg effect appears to impair principally the process of hormone release rather than its biosynthesis or storage.*	
Hyperparathyroid UK Action 4 Change	Guideline	7	5 - 6	1.3.10 Post op care is so important to be stressed as a necessity. So often we have members coming to us in panic with symptoms of low calcium in the days post op and their doctors have nothing to act on as they have no idea of the patients' levels. It is also imperative that this section needs considerably more than one sentence for post-operative care. Not only do they need to know their post op levels before discharge, they need to have advice in	Thank you for your comment. We have added a sentence to the committee's discussion of the evidence to evidence report K on making people aware of what signs and symptoms to watch out for following surgery. Recommendation 1.8.5 specifies that the clinician should discuss ongoing care and monitoring for primary hyperparathyroidism, explaining the type and frequency of monitoring that will be offered and the purpose of each.

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				preparation for hypocalcemia symptoms as well as instruction for calcium, vitamin D and magnesium supplements to eliminate these symptoms. Far too many patients are currently discharged with no advice and have to come to a support group for help they should be given by their surgeons before discharge. Untreated hypocalcemia post parathyroidectomy can result in tetany in worse cases and emergency trips to A&E for IV calcium and magnesium which more often than not is preventable with adequate preventative advice.	
Hyperparathyroid UK Action 4 Change	Guideline	7	5 - 6	1.3.10 Include how to manage low calcium post op, this so often doesn't happen with necessary visits to A&E for our group members. The lack of post op advice is inexplicable even by some of the surgeons who perform the highest number of surgeries. We are the ones they turn to with post-surgery calcium crash after their surgeon has said they will not need calcium. A surgeon can't predict how their patients will react to surgery in the first few days. They alert patients before surgery of worst case scenarios and the patient signs a consent form to proceed, but there is, more often than not, no mention of what can happen post op once the patient is discharged from the hospital. We believe it is important for the patient as well as for primary care to be aware of treatment, as patients are discharged into their care. For patients discharged in the evenings or weekends they have no point of call other than A&E. Some simple advice regarding a need for calcium, vitamin and magnesium might save them	Thank you for your comment. Recommendation 1.8.5 specifies that the clinician should discuss ongoing care and monitoring for primary hyperparathyroidism, explaining the type and frequency of monitoring that will be offered and the purpose of each. The management of hypocalcaemia was not prioritised during the scoping process of this guideline.

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				suffering with no-where to turn, faced with worrying post op symptoms of vibrating, tingling, pins and needles, cramping fingers and jitters. One of our members has suggested just adding the name of our organisation here for patients needing help.	
Hyperparathyroid UK Action 4 Change	Guideline	7	5 - 6	We are very concerned at the lack of any post-operative advice that all patients should be made aware of before discharge following their surgery. We are especially concerned for those who have vitamin D deficiency, low vitamin D, patients who may be unaware of hypomagnesemia , patients who are not forewarned of low calcium symptoms, patients who are not offered advice should they experience these symptoms, patients who are not given supplements to take in the first week post-surgery and patients who are not advised of their post op calcium, PTH, vitamin D and magnesium levels should they need to contact 111 or A&E within the days following surgery due to low calcium, low PTH, hungry bone syndrome, hypomagnesemia. We see cases often and are on hand to help those people who are in a situation which can be very frightening for the patient. An appropriate recommendation would be a valuable and necessary addition to this guideline. *Sudden suppression of parathyroid hormone (PTH), caused by successful parathyroidectomy, in patients with preoperative high levels of PTH and hypercalcaemia from enhanced bone turnover, may induce severe postoperative*	Thank you for your comment. We have added a sentence to the committee's discussion of the evidence in evidence report K on making people aware of what signs and symptoms to watch out for following surgery. Recommendation 1.8.5 specifies that the clinician should discuss ongoing care and monitoring for primary hyperparathyroidism, explaining the type and frequency of monitoring that will be offered and the purpose of each. Long-term management through supplementation was not prioritised during the scoping process of this guideline.

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				hypocalcaemia that may lead to symptoms of tetany. This relatively uncommon condition is known as "hungry bone syndrome" (HBS) https://www.omicsonline.org/open-access/hungry-bone-syndrome-after-parathyroidectomy-for-primary-hyperthyroidism-2161-1076-4-168.pdf?fbclid=IwAR3GHxvf5iZnahicI5nVXUA4EzioUki-ytfssEehEwbL0ISvV6FXtE2HKrI	
Hyperparathyroid UK Action 4 Change	Guideline	7	5 - 6	Overall it was noticeable that there were no recommendation for immediate post-surgery aftercare, resulting for some discharged without calcium tablets to suffer with low calcium symptoms, which if left untreated can lead to tetany. This could be easily prevented if guidance was made to provide patients with a supply of appropriate calcium, vitamin D and magnesium supplements to take after successful surgery. There is a lack of knowledge amongst doctors about this, whereas in patient support groups you find that everyone has the same experience – calcium drops significantly on days 3-4 and that is when the risk of tetany is highest. Perhaps more research should be done about this common symptom?	Thank you for your comment. We have added a sentence to the committee's discussion of the evidence in evidence report K on making people aware of what signs and symptoms to watch out for following surgery. Recommendation 1.8.5 specifies that the clinician should discuss ongoing care and monitoring for primary hyperparathyroidism, explaining the type and frequency of monitoring that will be offered and the purpose of each. Long-term management through supplementation was not prioritised during the scoping process of this guideline.
Hyperparathyroid UK Action 4 Change	Guideline	7	7 - 8	PTH, vitamin D and magnesium should also be measured 3 to 6 months after surgery to ensure that the patient has been cured and that the remineralisation of their bones is not going to be hindered by insufficient vitamin D or magnesium. This should be part of post-operative care recommendation for every patient, by every conscientious surgeon who wants the best for their patients' recovery.	Thank you for your comment. We recommend to measure PTH before discharge after surgery and measure calcium 3–6 months after surgery. This combination of test will confirm if the person has been cured. The committee did not consider from their knowledge and experience that another PTH test should routinely be offered. However, if the patient's post-operative

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					calcium fell within the realms of PHPT, retesting of PTH would occur, i.e. calcium above 2.5 with symptoms /2.6 without symptoms, as per recommendations on monitoring. Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function. This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/ hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects on PTH secretion or function in PHPT. We have added this to the committee's discussion of the evidence.
Hyperparathyroid UK Action 4 Change	Guideline	7	7 - 8	There is no mention at all about what a patient should do between discharge and 3 months which is the period when a majority of patients need advice as their body is re-mineralising. We recommend an insertion here offering advice for the benefit of the patient and primary care doctors who on the whole have no knowledge. Advice should include blood tests for calcium, PTH, vitamin D and magnesium in order for primary care doctors to be equipped on how to treat symptoms experienced in this period of adjustment for many who have had primary hyperparathyroidism for a good many years and whose body is thrown into a state of shock and readjustment while levels normalise.	Thank you for your comment. We have added a sentence to the committee's discussion of the evidence in evidence report K on making people aware of what signs and symptoms to watch out for following surgery. Recommendation 1.8.5 specifies that the clinician should discuss ongoing care and monitoring for primary hyperparathyroidism, explaining the type and frequency of monitoring that will be offered and the purpose of each.
Hyperparathyroid UK Action 4 Change	Guideline	7	9 - 11	1.3.12 A patient should be monitored as a minimum, at 3 months and 6 months after	Thank you for your comment. In the absence of evidence the committee used their knowledge and

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				surgery, then annually for 2 two years to include a follow up dexa bone density scan including non-dominant forearm to determine benefits to bone density of parathyroid surgery. .Follow-up monitoring is essential to ensure the success of surgery as recovery can take up to a year for some people before calcium and PTH levels have settled. For research purposes (which a need for, has already been highlighted, this makes perfect sense also, especially considering the post op questionnaires used for your consultation were so out of date and focused on voice issues),	expertise to make recommendations on monitoring. Calcium would be measured annually when a blood test is ordered for another reason. We have amended recommendation 1.4.12 to monitor calcium no more frequently than once a year in people who have had successful surgery.
Hyperparathyroid UK Action 4 Change	Guideline	7	9 - 11	1.3.12 I prefer to monitor at 6 and 12 months as a minimum. The later Table discusses follow-up of multi-gland disease, leaving it to specialist opinion	Thank you for your comment. There was no evidence for a specific timepoint. The committee considered this should be done within 6 months but wanted to be more permissive and hence opted for 3-6 months. We have amended recommendation 1.4.12 to monitor calcium no more frequently than once a year instead of only when a blood test is being taken for another reason.
Hyperparathyroid UK Action 4 Change	Guideline	7	9 - 11	1.3.12 Calcium can take a long time to stabilise post-surgery. For someone like me, who had an initial calcium of 5.69 mmol/litre pre-surgery, I would have been horrified if I had not been regularly monitored post-surgery. Whilst my calcium has at times fallen within the reference range, it has also fallen below the reference range. I feel much more reassured knowing that my calcium will continue to be monitored at least annually for the rest of my life, as the medical professionals have no idea how quickly my calcium rose or how quickly my adenoma grew in the first place. Until further research has been completed in this area, it	Thank you for your comment. There was no evidence for a specific timepoint. The committee wanted this to be done within 6 months but wanted to be more permissive and hence opted for 3-6 months. We have amended recommendation 1.4.12 to monitor calcium no more frequently than once a year instead of only when a blood test is being taken for another reason.

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				would be better if guidelines suggested three consecutive normal readings of calcium and PTH over a period of 3-6 months, and thereafter annual monitoring of calcium and PTH.	
Hyperparathyroid UK Action 4 Change	Guideline	7	9 - 11	1.3.12 We are concerned that this post op testing advice at 6 months does not specify for testing pth at same time. This should specify that surgery cannot be determined if successful if the pth has not fallen to a correlating/suppressive pattern at same time. The standalone calcium level does not indicate if parathyroid glands are now functioning correctly. Please make clearer for primary care to understand.	Thank you for your comment. The committee from their experience discussed that patients are considered to be biochemically cured if their PTH is in the reference range immediately following surgery and their serum calcium is within the reference range 3–6 months after surgery. Overall the committee did not think that a PTH test at 3–6 months would offer any additional clinical value. The committee noted that persistently high calcium at 3–6 months would trigger testing of plasma PTH (as per the recommendations on diagnosis).
Hyperparathyroid UK Action 4 Change	Guideline	7	9 - 11	1.3.12 In my opinion, a patient should be monitored for a minimum of 6 months after surgery and then annually for at least two years. Follow-up monitoring is not only essential but critical to ensure the success of surgery. The body can take time to adjust to the effects of surgery. It can take up to a year for some, before calcium and PTH levels have settled. Additionally, there is also the risk of hypocalcaemia following parathyroid surgery which needs to be monitored and this can also take time to settle. By monitoring regularly, inconsistencies can be identified earlier and whether the surgery has been a success can be assessed with full information. To stop monitoring after six months seems premature and short-sighted and not in the long-term interest of the patient.	Thank you for your comment. We have amended recommendation 1.4.12 to monitor calcium no more frequently than once a year instead of only when a blood test is being taken for another reason.
Hyperparathyroid UK	Guideline	7	9 - 11	If a patient remains symptomatic post op or	Thank you for your comment.

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Action 4 Change				symptoms return after a few weeks or months of relief, and adjusted serum calcium is higher than it was post op, a further calcium test with concurrent PTH should be undertaken.	A persistently high calcium at 3–6 months would trigger testing of plasma PTH (as per the recommendations on diagnosis).
Hyperparathyroid UK Action 4 Change	Guideline	7	9 - 11	It is often apparent within the first weeks for those unfortunate people for whom surgery was not a success, or alternatively, some experience an amazing relief of symptoms only for some of them to return with 3 or 4 months. This is when magnesium, vitamin D, calcium and PTH need to be checked to rule out a deficiency as a cause of a return of similar symptoms. Once ruled out, consideration should be taken to monitor these people sooner. Let us remember the impact on a person's quality of life of living in hope of a cure only to find surgery was unsuccessful and they are back to the drawing board (with scar tissue). These people need assurances that all is not lost, they are not abandoned without hope and steps will be taken to find out why surgery was unsuccessful so that a re-op can occur in 6 months (for scar tissue to repair) . Ask a symptomatic patient with primary hyperparathyroidism what 6 months feels like, and they will likely respond 6 years.	Thank you for your comment. There was no evidence for a specific timepoint. The committee considered this should be done within 6 months but wanted to be more permissive and hence opted for 3-6 months.
Hyperparathyroid UK Action 4 Change	Guideline	7	15 - 19	1.3.13 Multidisciplinary teams must be brought up to speed with these guidelines and have a broad understanding of hyperparathyroidism and its effect on a patient's quality of life and long term health before making a decision. Personally and from experience within our organisation in the past, this decision is better placed between the patient and her trusted surgeon rather than a multidisciplinary team	Thank you for your comment. In the knowledge and experience of the committee a multidisciplinary review offers the person the best possible opportunity of improving outcomes, for example after repeat surgery. This does not replace the discussion between the surgeon and the person regarding the benefits and risks of further surgery.

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				who ought only to be consulted should the patient and surgeon not be able to agree on a treatment plan. In our experience we know of multidisciplinary teams who have on several occasions made decisions that were not in the patients best interests and they had to go out of their area for a 2nd opinion which resulted in surgery they had been denied based on the decision of MDT.	
Hyperparathyroid UK Action 4 Change	Guideline	7	20	We are concerned that the guidelines are advising monitoring in preference to repeat surgery. It is not very clear on the guideline document alone why this would be the case? As stated in page 19, line 4 of evidence F, surgery is the only definitive cure. All patients regardless of age deserve the chance to be cured by surgery. It is not within their control whether surgery would be successful or not. There are many variables as to why surgery is unsuccessful; surgeon error, adenoma missed, ectopic glands, none of which is patients' fault. Has any research been included of numbers of re-op patients who have had this done privately, often with same surgeons who also operate on the NHS? Why should only those who can afford it be able to be cured from this disease and its long-term health complications?	Thank you for your comment. The recommendations do support repeat surgery if that is recommended by the multidisciplinary review.
Hyperparathyroid UK Action 4 Change	Guideline	7	20	We are concerned that monitoring is recommended following a failed surgery. We have seen many cases where a conscientious surgeons very disappointed to have to tell a patient he did not succeed in finding the adenoma, and steps have been taken to rescan looking for ectopic glands and then	Thank you for your comment. We recommend a multidisciplinary review is undertaken in conjunction with monitoring. This monitoring might be until further surgery has taken place or may be longer term depending on the individual circumstances.

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				proceeded to successfully perform a 2nd or in some cases a third surgery. Also we have of course seen cases where our members sought a 2nd opinion with an alternative surgeon for a successful re-op. Our mantra is 'Never Give UP. We so happy for a member who finds the strength and determination to fight for a 2nd surgery and achieve success and renewed quality of life. It is very disheartening to see you recommend that they do actually admit defeat and give up. Based on positive outcomes we cannot support this. I would like to hear if Professor John Wass of the Getting it Right First Time Panel (GIRFT) has an opinion on how to get it right first time. Whatever happened to 'If at first you don't succeed, try, try, try again?' obviously we don't mean unnecessarily repeated surgeries but this is an instance where 4D CT and Fluoride Spect scans can become invaluable.	
Hyperparathyroid UK Action 4 Change	Guideline	7	20	Table 1. Repeat surgery should be offered rather than monitoring. We have seen cases where ectopic glands not found first time where conscientious surgeons offered repeat scans and a second surgery at 6 months to allow for scar tissue to heal. It is the responsibility of the surgeon to offer further imaging and a 2nd attempt at surgery. An experienced surgeon will examine the carotid sheath and the thymus if a gland is not in the expected location.	Thank you for your comment. We recommend a multidisciplinary review is undertaken in conjunction with monitoring. This monitoring might be until further surgery has taken place or may be longer term depending on the individual circumstances.
Hyperparathyroid UK Action 4 Change	Guideline	8	3 - 5	***We recommend an inclusion here to alert of changes in serum magnesium levels during cinacalcet therapy for primary hyperparathyroidism.***	Thank you for your comment. Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function. This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/hypocalcaemia.

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				The calcium receptor (CaR) participates in Ca2+ and Mg2+ metabolism at the parathyroid gland and the kidney. Cinacalcet, a calcimimetic, increases the sensitivity of CaR and has been introduced for the treatment of patients with primary hyperparathyroidism (PHPT). However, there are no data for the influence of cinacalcet on serum Mg2+ levels in the literature. *Aim: To evaluate the effect of cinacalcet treatment on magnesium levels in patients with primary hyperparathyroidism.* *Methods: Sixteen patients, aged 65±11 years with primary hyperparathyroidism receiving cinacalcet therapy were enrolled in the study. Six patients were diagnosed with parathyroid adenoma and ten patients with parathyroid hyperplasia. Median daily cinacalcet dose was 60 mg (range 30–90 mg). Patients were evaluated for a period of 2–8 months. Adverse effects of the drug were reported and serum calcium and magnesium were determined.* *Results: During cinacalcet therapy thirty eight percent of patients reported cramps with normal CPK, 12% myalgia, and 12% atrial arrhythmia. Mean serum calcium levels were reduced to the normal range (P<0.0001) within the first 2 weeks of treatment and remained constant throughout the study in all patients. The reduction was dose-dependent (P<0.0001). Serum magnesium concentrations were significantly reduced in 14 patients (88%), (P=0.03). The reduction was also dose-dependent (P=0.006). In contrast to Ca levels a time-dependent fluctuation of Mg2+ at steady*	The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects on PTH secretion or function in PHPT. We have added this to the committee's discussion of the evidence.

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				state was observed. Ca2+ and Mg2+ serum levels changes were highly correlated at all doses (r=0.9; P=0.037). *Conclusions: Cinacalcet treatment in patients with primary hyperparathyroidism results in normal serum Ca2+levels but reduces the Mg2+ serum levels below normal values in the majority of the patients. Hypomagnesemia may cause symptoms like cramps, myalgia, and arrhythmia. It has been stated that activation of the CaR in the thick ascending limb of loop of Henle leads to reduced reabsorption of Ca2+ and Mg2+ and activating CaR mutations result in hypomagnesemia in some patients. Cinacalcet is responsible for the reduction both calcium and magnesium levels and may cause the reported adverse effects.* https://www.endocrine-abstracts.org/ea/0026/ea0026OC3.2.htm?fbclid=IwAR0xD0Dk8-gyFItaSCUbSW3IcMavvEXc7jVBBxl-QDKzb_NuBJpQ7zBrR0o	
Hyperparathyroid UK Action 4 Change	Guideline	8	3 - 7	1.4.1 Again, not sure where the threshold of 2.85mmol/L comes from, as I am not aware of any evidence that symptoms or long-term complications are directly linked to the height of serum calcium above the PRR. Indeed, my experience is that the renal stone disease and osteoporosis groups frequently have calcium below that threshold. If surgery is liberally used, this will be a small group (requiring cinacalcet as primary therapy), but I suspect that economic considerations are predominant here. There is no mention of using cinacalcet to treat severe hypercalcaemia prior to	Thank you for your comment. Cinacalcet acts to decrease serum calcium and therefore the committee considered the largest benefit would be in people with an adjusted serum calcium level above the reference range. Therefore, most benefit will be achieved in people with a high serum calcium level and symptoms resulting from their hypercalcaemia. It would also lower the risk of end organ damage. The recommendation does allow for the use of calcimimetics prior to surgery.

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				proposed surgery, but I guess that is the remit of specialist opinion.	
Hyperparathyroid UK Action 4 Change	Guideline	8	3 - 7	1.4.1 Cinacalcet is *not* suitable for *everyone* with a calcium level of 3.0mmol/litre or above. I was prescribed IV cinacalcet by my endocrinologist in hospital when I presented with a calcium level of 5.69mmol/litre and a PTH level of 999pg/ml. Whilst this reduced my dangerously high calcium level, it caused *extreme* pain in my bones as my PTH was still very high and calcium was being leeched from my bones. Post-surgery, I required physiotherapy to move again because of the damage done by the cinacalcet. My surgeon believed with levels this high urgent/emergency surgery is a much more appropriate option. Guidelines should reflect this.	Thank you for your comment. The committee agree that cinacalcet is not suitable for everyone with a calcium over 3 mmol/litre and it should not be considered an alternative to surgery. The recommendations are required for example for people who choose not to undergo surgery.
Hyperparathyroid UK Action 4 Change	Guideline	8	3 - 7	1.4.1 Patients diagnosed with primary hyperparathyroidism and deemed suitable for surgery must not be declined surgery unless unsuitable for surgery based on a risk assessment e.g. due to other health conditions. Surgery must always be the preferred option to treat primary hyperparathyroidism due to its curative rate. Non-surgical options such as medication do not cure patients, and consequently impact their quality of life.	Thank you for your comment. Recommendation 1.3.2 considers referral to a surgeon in people with a confirmed diagnosis of PHPT. We have amended 1.4.6 and now refer to a discussion of the risks and benefits of each approach (to surgery).
Hyperparathyroid UK Action 4 Change	Guideline	8	3 - 7	Patients diagnosed with primary hyperparathyroidism and deemed suitable for surgery must not be declined surgery. If they are deemed unsuitable for surgery based on a risk assessment e.g. due to other health conditions then that is a different matter.	Thank you for your comment. Recommendation 1.3.2 considers referral to a surgeon in people with a confirmed diagnosis of PHPT. We have amended 1.4.6 and now refer to a discussion of the risks and benefits of each approach (to surgery).

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				Surgery must always be the preferred option to treat primary hyperparathyroidism due to its curative nature. Non-surgical options such as medication do not cure patients, they only manage them and consequently will impact the quality of life of these patients.	
Hyperparathyroid UK Action 4 Change	Guideline	8	3 - 7	If a patient with primary hyperparathyroidism has unsuccessful surgery or is unsuitable for, or has been declined surgery they will likely need cinacalcet before their albumin-adjusted serum calcium level reaches 3.0 mmol/litre or above as they are at risk for stroke and heart attack if their calcium levels are that high, If the patient is going to benefit from some symptom relief, why prolong their suffering waiting for a level that may never quite hit 3mmol/l? As we know calcium is likely fluctuating, it could well hit this level on days it isn't tested so this is unreasonable.	Thank you for your comment. Cinacalcet acts to decrease serum calcium and therefore the committee considered the largest benefit would be in people with an adjusted serum calcium level above the reference range. Therefore, most benefit will be achieved in people with a high serum calcium level and symptoms resulting from their hypercalcaemia. It would also lower the risk of end organ damage.
Hyperparathyroid UK Action 4 Change	Guideline	8	6 - 7	These thresholds are too high and many will suffer needlessly. Whilst we are aware cinacalcet was originally licensed for patients with calcium >3mmol/l, we know of people who have had relief from symptoms with much lower levels. In other instances many people have experienced debilitating nausea and sickness taking cinacalcet. A number of our members have found they simply could not tolerate the side effects of cinacalcet. It really should only be considered in the short term for patients finding it hard to tolerate.	Thank you for your comment. Cinacalcet acts to decrease serum calcium and therefore the committee considered the largest benefit would be in people with an adjusted serum calcium level above the reference range. Therefore, most benefit will be achieved in people with a high serum calcium level and symptoms resulting from their hypercalcaemia. It would also lower the risk of end organ damage.
Hyperparathyroid UK Action 4 Change	Guideline	8	6 - 7	The thresholds of 2.85 and 3.0 for serum calcium levels are arbitrary and historic. They are way too high for someone who has high calcium and high PTH but is deemed	Thank you for your comment. Cinacalcet acts to decrease serum calcium and therefore the committee considered the largest benefit would be in people with an adjusted serum calcium level above the reference

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				unsuitable for surgery. I doubt that someone with a calcium level 3.0 or higher would be truly asymptomatic. They are more likely to have symptoms they are not aware of or had them a long and not attributed them to hypercalcaemia. In the case where a patient has a serum calcium level of 2.70 and demonstrates symptoms but is unable to have surgery, what is the proposed treatment plan? Will such a patient be denied Cinacalcet??? Hypercalcemia is a silent killer like heart disease.	range. Therefore, most benefit will be achieved in people with a high serum calcium level and symptoms resulting from their hypercalcaemia. It would also lower the risk of end organ damage.
Hyperparathyroid UK Action 4 Change	Guideline	8	17 - 18	It would be helpful to add here 'because it increases the chances of bone fracture', We believe primary hyperparathyroidism should be ruled out as a cause for osteoporosis before proceeding with bisphosphonate treatment and a cautionary note should be added to the 'bisphosphonates for treatment of osteoporosis' guideline.	Thank you for your comment. It is not within our remit to edit the bisphosphonates for treatment of osteoporosis guideline. If the guideline we have drafted had been followed, people with the test results you describe would be diagnosed with primary hyperparathyroidism . There are a number of reasons for which bisphosphonates are not recommended for chronic use in primary hyperparathyroidism but increased risk of bone fracture is not the primary one.
Hyperparathyroid UK Action 4 Change	Guideline	8	17 - 18	This UCLA study finds using drugs to combat hyperparathyroidism is worse than doing nothing at all: *'Doctors commonly treat hyperparathyroidism using a class of prescription drugs called bisphosphonates, including alendronate (marketed under the brand name Fosamax) and ibandronate (Boniva), which are supposed to strengthen bones. Now, a study led by scientists at UCLA found that those drugs actually increase the risk of fracture, meaning that taking them is worse than doing nothing at all to treat the condition. The research also*	Thank you for your comment. The reference does not meet the evidence review protocol, which can be found in Appendix A of evidence report H. The committee recognised that surgery is the only cure for primary hyperparathyroidism but we also acknowledge the importance of bisphosphonates for reducing fracture risk. Recommendation 1.5.5 makes it clear that they should not be used for chronic hypercalcaemia.

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				revealed that patients who have surgery to remove the overactive parathyroid glands have fewer subsequent bone fractures' http://newsroom.ucla.edu/releases/for-treating-a-leading-cause-of-osteoporosis-surgery-is-better-than-widely-used-medications?fbclid=IwAR2x5wX6hYIChRSniCWV8hOPoXsRTHVeQmBpkxY9HAKanDEVw_GnYXeSkMU	
Hyperparathyroid UK Action 4 Change	Guideline	9	4	1.5.1 Table 1. This table needs to be rethought! Where will you put all the thousands of people diagnosed with primary hyperparathyroidism with calcium between 2.5mmol/l and 2.84mmol who you have condemned to not fitting the eligibility criteria for surgery, or cinacalcet? Pretty much where most of them are right now I guess? Stuck in limbo, suffering debilitating symptoms and consequences of untreated primary hyperparathyroidism. The reason we campaigned for these guidelines is to improve this void that thousands fall into. I hope these are the people who you aimed to help in page 1 line 7, although the missing word after managing is 'curing': '*This guideline covers diagnosing, assessing and managing primary hyperparathyroidism. It aims to improve recognition and treatment of this condition, reducing long-term complications and improving quality of life'*	Thank you for your comment. We have edited the table to direct people to the recommendations (actions) that should be taken given a positive monitoring test. The specified group can be considered for surgery according to recommendation 1.3.2.
Hyperparathyroid UK Action 4 Change	Guideline	9	4	1.5.1 Monitoring. In the column for people who have had a successful parathyroid surgery, *'Consider opportunistic monitoring of albumin-adjusted serum calcium if the person has a routine blood test, no more than once a year'*	Thank you for your comment. The committee from their experience discussed that patients are considered to be biochemically cured if their PTH is in the reference range immediately following surgery and their serum calcium is within the reference range 3–6 months after

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				needs to be amended to include *'after the first 12 months post-surgery' because until treatment throughout the UK becomes more regulated with improved success rates, there remains an element of uncertainty for the first 12 months due to not testing intraoperative PTH, not checking all 4 glands, or even the ongoing chance that remaining glands can indeed begin to malfunction once the dominant adenoma is removed.*	surgery. The committee considered that the risk of recurrent disease following successful removal of a solitary adenoma is very low and that, after the 6-month check, it is sufficient for calcium to be checked as part of routine blood testing to a maximum once a year. We have amended recommendation 1.4.11 to monitor calcium no more frequently than once a year in people who have had successful surgery. The committee highlighted that for people with multiple gland disease there is a higher risk of recurrence than in those who had a single adenoma and in monitoring of such patients specialist opinion should be sought. However, the committee noted that the risk is still very low if the person has normal adjusted calcium at 3 to 6 months after surgery. The committee noted that persistently high calcium at 3–6 months would trigger testing of plasma PTH (as per the recommendations on diagnosis).
Hyperparathyroid UK Action 4 Change	Guideline	9	4	1.5.1 Monitoring - Calcium, Vitamin D, PTH and Magnesium in the same blood draw to check the correct suppressive relationship and any effect hypomagnesemia may be having on vitamin D and PTH.	Thank you for your comment. We do recommend that calcium should be taken at the same time as PTH (recommendation 1.1.6). We could not recommend Vitamin D and magnesium testing as part of monitoring as this was not prioritised for inclusion in the review protocol for this question.
Hyperparathyroid UK Action 4 Change	Guideline	9	4	Column 2: And PTH Dexa annually until osteopenia negated	Thank you for your comment. In the absence of evidence the committee used their knowledge and experience to form this recommendation. They carefully considered the benefits and risks of the timing interval for DXA scans in conjunction with a consideration of costs.
Hyperparathyroid UK	Guideline	9	4	Table 1. Colum 2. Patients should be offered	Thank you for your comment. Psychological

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Action 4 Change				CBT for the 'psychological' aspects of the disease and the impact on the patients wellbeing while waiting for surgery or in between surgeries, such as how it affects other aspects of their life; working, relationships, including ability to have a physical relationship and effect on fertility, the effect on family members and being able to care for themselves, all which greatly impact on quality of life.	interventions were not raised by stakeholders during scoping.
Hyperparathyroid UK Action 4 Change	Guideline	9	4	Column 3: Where are these experts? From experience we have a few listed on our website but they are few and far between. There is much learning to be done at endocrine level. We are currently trying to teach them, which actually feels wrong. We are supposed to be under their care and guidance.	Thank you for your comment. NICE guidelines are not able to recommend specific health professionals, but local referral pathways will guide the clinician on who to refer to.
Hyperparathyroid UK Action 4 Change	Guideline	9	4	Scan pre-op and follow up post op to ensure the bone is rebuilding, 3 years is too long for the first follow up.	Thank you for your comment. In the absence of evidence the committee used their knowledge and experience to form this recommendation. They carefully considered the benefits and risks of the timing interval for DXA scans in conjunction with a considered of costs.
Hyperparathyroid UK Action 4 Change	Guideline	9	4	Table 1. I disagree with the recommendation of only testing calcium annually for people who have either not had surgery or had unsuccessful surgery (unless on cinacalcet). I actually believe this suggestion could endanger life and ought to be revised. If a person is not on cinacalcet and their levels increase to a level where cinacalcet or an IV infusion is needed to bring down calcium levels, how would they know if their blood is only being monitored annually? Surely more regular monitoring is better for the patient than	Thank you for your comment. The committee considered that the risk of recurrent disease following successful removal of a solitary adenoma is very low and that, after the 6-month check, it is sufficient for calcium to be checked as part of routine blood testing to a maximum of once a year. We have amended recommendation 1.4.11 to monitor calcium no more frequently than once a year in people who have had successful surgery. The committee highlighted that for people with multiple gland disease there is a higher risk of recurrence than in those who had a single adenoma and in monitoring of such patients specialist

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				an emergency ambulance to A&E? You are surely aware of the risks of long term hypercalcemia with PHPT? This is an extract from an article by the European Society of cardiology on Primary Hyperparathyroidism and heart disease, a review: *It has been reported that patients suffering from symptomatic pHPT have increased mortality, mainly due to an overrepresentation of cardiovascular death. pHPT is reported to be associated with hypertension, disturbances in the renin—angiotensin—aldosterone system, and structural and functional alterations in the vascular wall. Recently, studies have indicated an association between pHPT and heart disease.* Please read the article: https://academic.oup.com/eurheartj/article/25/20/1776/497057	opinion should be sought. The committee noted that persistently high calcium at 3–6 months would trigger testing of plasma PTH (as per the recommendations on diagnosis). For people who have disease that recurs after successful surgery, the committee recommend to seek specialist endocrine opinion on monitoring. The committee discussed the increased risk of mortality due to cardiovascular causes both before and after parathyroidectomy and hence considered that there is a need for monitoring cardiovascular risk in this group of patients.
Hyperparathyroid UK Action 4 Change	Guideline	9	4	Table 1. Include osteopenia as well as osteoporosis. So many of our members have osteopenia which leads to osteoporosis whilst they are waiting for surgery.	Thank you for your comment. DXA is recommended as part of assessment in our recommendations. A referral would be made if low bone density is identified (rather than osteopenia). We consider overarching fracture risk, including bone density, to determine management strategy.
Hyperparathyroid UK Action 4 Change	Guideline	9	4	Table 1. And PTH as one without the other is useless	Thank you for your comment. If the level of calcium is 2.6 mmol/litre or 2.5 mmol/litre with symptoms then a PTH test would be conducted. We have now directed people to these recommendations in the table.
Hyperparathyroid UK Action 4 Change	Guideline	9	4	Under 'People who have had successful parathyroid surgery', some people need	Thank you for your comment. In the knowledge and experience of the committee hypercalcaemia is

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				monitored more than once a year, even if they have had successful surgery. Particularly concerning is the possibility of low calcium following surgery. Needs further guidance about how and when you determine surgery has been successful. Again, I'd suggest three consecutive normal readings of calcium and PTH over a period of 3-6 months, and thereafter annual monitoring of calcium and PTH, unless the patient becomes symptomatic again. Also, monitoring of calcium alone is not always enough. If symptomatic, PTH should always be tested with calcium.	unlikely to develop as a late complication of successful surgery. If the level of calcium is 2.6 mmol/litre or 2.5 mmol/litre with symptoms then a test for PTH would be conducted. We have now directed people to these recommendations in the table.
Hyperparathyroid UK Action 4 Change	Guideline	10	2 - 4	1.6.1 We are concerned that you have advised here to '*Offer parathyroid surgery to women who have primary hyperparathyroidism and are considering pregnancy',* yet on lines 5-6 you recommend management of primary hyperparathyroidism for pregnant women when in fact you should be recommending surgery to protect mother and baby. You warn on page 26, line 4 of high risk of neonatal complications.	Thank you for your comment. Surgery for a woman who is diagnosed with PHPT when pregnant should be discussed with the context of a multidisciplinary team. The risks and benefits would be discussed on a case-by-case basis.
Hyperparathyroid UK Action 4 Change	Guideline	10 11	3 - 23 2 – 66	I'm a bit confused by the messages here. Section 1.6.1 suggests women with HPT considering pregnancy have surgery before pregnancy, which seems to imply that HPT is not a good thing during pregnancy, and I agree with that. But then, 1.6.7 suggests they are told that 'HPT doesn't affect the baby before or after birth', which seems to contradict the earlier message. In fact, there are studies showing a higher than expected rate of hypertensive disease (which is often harder to treat), which itself is associated with poorer	Thank you for your comment. We have removed recommendation 1.6.7.

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				foetal outcomes, and of higher rates of miscarriage and stillbirth, in patients with HPT. I accept that there is little hard evidence that surgery during pregnancy reverses these, but that would be a very difficult research hypothesis to test, and I would have liked to see more advice on the role of surgery during pregnancy, as this is a very difficult issue. Good that a multidisciplinary team is recommended, though, and that research into this should be done.	
Hyperparathyroid UK Action 4 Change	Guideline	10	5 - 6	1.6.2 These lines suggesting management of primary hyperparathyroidism in pregnant women suggest a contradiction based on available evidence within the rationale of the dangers during pregnancy. Telling GP's to advise pregnant women there is no danger to baby either before or after birth is incorrect, dangerous to both mother and child, and also misleading. Guideline page 26, line 4 states high risk of neonatal complications.	Thank you for your comment. We have removed recommendation 1.6.7.
Hyperparathyroid UK Action 4 Change	Guideline	10	5 - 6	Please read in full this 2018 UK pilot study of 289 women and consider amending section 1.6.2 accordingly. Here is an abstract taken from the study: Primary hyperparathyroidism (pHPT) in pregnancy is reported to be associated with significant maternal and foetal complications and an up to threefold increase in the risk of miscarriage. *Methods: Following UK National ethics committee approval, women who had experienced 3 or more consecutive*	Thank you for your comment. We have circulated the reference to the guideline committee.

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				miscarriages were recruited from a nationwide RM clinic. Serum corrected calcium, phosphate, PTH and vitamin D were evaluated. Patients with raised serum calcium and/or PTH were recalled for confirmatory tests. Power calculations suggested that a minimum of 272 patients were required to demonstrate a clinically significant incidence of pHPT. *Results: Three hundred women were recruited, median age 35 years (range 19–42). Eleven patients had incomplete data, leaving 289 patients suitable for analysis; 50/289 patients (17%) with abnormal tests were recalled. The prevalence of vitamin D deficiency (<25 nmol/l) and insufficiency (25–75 nmol/l) was 8.7 and 67.8%, respectively. One patient was diagnosed with pHPT (0.34%) and underwent successful parathyroidectomy.* *Conclusions: The prevalence of undiagnosed pHPT (0.34%) in RM in this study appears to be many times greater than the 0.05% expected in this age group. The findings of this pilot study merit follow-up with a larger-scale study. Routine serum calcium estimation is not currently undertaken in RM and should be considered.*	
Hyperparathyroid UK Action 4 Change	Guideline	10	5 - 6	*HPT during pregnancy is under recognized and is associated with a 3·5-fold increase in miscarriage rates. Pregnancy loss often occurs in the second trimester and is associated with multiple miscarriages when not addressed.*	Thank you for your comment. We have made the committee aware of the reference.

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				Pregnancy loss is more common as calcium levels exceed 11·4 mg/dl (2·85 mmol/l), ***but can be seen at all elevated calcium levels.*** *Emphasis is placed on earlier recognition and surgical cure before becoming pregnant, however, once pregnant, surgery should be offered early in the second trimester for those with calcium levels above 11·4 mg/dl.(2.85mmol/l) taken from this 2009 study: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2265.2008.03495.x*	
Hyperparathyroid UK Action 4 Change	Guideline	10	5 - 6	Maternal complications in patients with hyperparathyroidism can be as high as 67% according to this 2011 study: https://www.tandfonline.com/doi/abs/10.1080/08998280.2011.11928719	Thank you for your comment. The committee recognised that the rate of maternal complications may be high and agreed that a multidisciplinary team would offer the best opportunity to improve patient outcomes.
Hyperparathyroid UK Action 4 Change	Guideline	10	5 - 6	This text advising against management of primary hyperparathyroidism in pregnancy in favour of surgery is taken from the study to follow. Please read it and amend lines 5-6 accordingly: '*Primary hyperparathyroidism pregnancy poses significant risks to the mother and the foetus. Fortunately, prompt diagnosis and effective management can improve outcomes for both. There is controversy regarding appropriate management of these patients, especially late in gestation. The objective of this article, therefore, is to review the literature and to propose an evidence-based approach to managing these patients*' https://journals.lww.com/obgynsurvey/Abstract/2002/06000/Primary_Hyperparathyroidism_in.	Thank you for your comment. Recommendation 1.7.1 offers surgery to all women with PHPT who are considering pregnancy. Recommendation 1.7.2 covers women who are diagnosed with PHPT when pregnant. The risks and benefits of surgery will depend on the individual circumstances.

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				22.aspx	
Hyperparathyroid UK Action 4 Change	Guideline	10	18 - 21	We are concerned that you recommend to refer pregnant women with hyperparathyroidism and hypertension to the guideline on hypertension in pregnancy, when the reality is that hyperparathyroidism is a probable cause of the hypertension. Hyperparathyroidism in pregnancy poses a significant risk to both mother and baby: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2265.2008.03495.x	Thank you for your comment. We cross refer to the hypertension in pregnancy guideline and did not cover this as a specific evidence review question. We are therefore unable to be more specific.
Hyperparathyroid UK Action 4 Change	Guideline	10	18 - 21	We recommend you read the following study about hyperparathyroidism in pregnancy and reconsider your recommendations: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3124907/?fbclid=IwAR3yVUQ3xoticNUP7iBf2QrFgY6xPdApmOi836P6rj2Kz0Kgkg_I5nZQlQk *Hunter and Turnbull documented the first case of hyperparathyroidism in pregnancy in 1931 (4, 5). It is theorized that the incidence of PHP in the pregnant patient is similar to that in the non-pregnant patient. PHP commonly goes unrecognized due to the physiological changes of pregnancy. Hypoalbuminemia, calcium transport across the placenta, and an increased glomerular filtration rate all contribute to the appearance of lower calcium levels in the pregnant patient. In addition, estrogen is thought to inhibit parathyroid hormone (PTH)–mediated bone resorption, causing a dose-related reduction in serum calcium in pregnancy (6). We present a case of a pregnant patient with chronic hypertension*	Thank you for your comment. The reference does not meet the evidence review protocol for the evidence review which can be found in appendix A of evidence report J. We have made the committee aware of the study.

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				that was exacerbated throughout the course of her pregnancy with a concomitant diagnosis of PHP and its sequelae for both the mother and foetus.	
Hyperparathyroid UK Action 4 Change	Guideline	10	18 - 21	This paper from The University of Malta confirms that parathyroidectomy performed in the third trimester of pregnancy is effective. Postponing surgery may risk an adverse maternal and foetal outcome: https://www.um.edu.mt/umms/mmj/PDF/308.pdf	Thank you for your comment. The reference does not meet the evidence review protocol for this question which can be found in appendix A of evidence report J. Surgery may be recommended as an option arising out of the multidisciplinary review.
Hyperparathyroid UK Action 4 Change	Guideline	11	12	Correct and consistent needs adding as it certainly isn't at the moment.	Thank you for your comment. The NICE guideline on patient experience (CG138) provides detail on how information should be provided. We cross refer to this guideline in recommendation 1.8.1.
Hyperparathyroid UK Action 4 Change	Guideline	11	17	Ensure a full list of common symptoms is shown	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have amended recommendation 1.1.2 to be inclusive of all non-differentiated symptoms associated with PHPT. We now list the common symptoms in the section 'terms used in this guideline' and in the committee's discussion of the evidence in evidence report A to reflect those mentioned in your comment on the most common symptoms.
Hyperparathyroid UK Action 4 Change	Guideline	11	25	*'Non-surgical treatments that are available'* suggests to patients that an adenoma can be treated in some way other than surgery, which isn't clear enough. This should read: Give people information about available treatment and management of primary hyperparathyroidism: • Surgical treatment is the only cure;	Thank you for your comment. We do not believe that the current wording implies that it is a cure. It is important that the person is made aware of all of the management options so that they can weigh up the benefits and risks of each form of treatment.

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				• Some symptoms may be managed non-surgically; • An emphasis that non-surgical management is effectively a sticking plaster for symptoms only, but the disease remains and will continue to cause long term damage and reduced lifespan.	
Hyperparathyroid UK Action 4 Change	Guideline	11	25	Exclude non-surgical as a 'treatment' as over 90% of surgical cases are cured despite my first endo telling me negatively that surgery is only curative in less than 50% of cases. (An example of how regulated education is needed at endocrine level). It should be amended to surgical treatments and non-surgical management.	Thank you for your comment. We do not believe that the current wording implies that it is a cure but it is a treatment. It is important the person is made aware of all of the management options so that they can weigh up the benefits and risks of each form of treatment.
Hyperparathyroid UK Action 4 Change	Guideline	12	7	What evidence points to exercise reducing the symptoms of primary hyperparathyroidism?	Thank you for your comment. In the knowledge and experience of the committee people ask if exercise will exacerbate their symptoms.
Hyperparathyroid UK Action 4 Change	Guideline	12	8	What evidence points to diet reducing the symptoms of primary hyperparathyroidism?	Thank you for your comment. In the knowledge and experience of the committee people ask if diet will exacerbate their symptoms or if a diet will help control symptoms. We have not defined the content of the information for any of the topics specified.
Hyperparathyroid UK Action 4 Change	Guideline	12	12	And calcium, magnesium supplementing in case of a calcium crash, there are a large number of our group who end up in A&E on drips as their calcium levels drop and they are at risk of tetany. This is costly to the NHS and could be avoided/reduced.	Thank you for your comment. The management of hypocalcaemia was not prioritised during the scoping process of this guideline.
Hyperparathyroid UK Action 4 Change	Guideline	12	12	Health care professionals need training in this too.	Thank you for your comment. We anticipate that these guidelines will raise awareness of PHPT.
Hyperparathyroid UK Action 4 Change	Guideline	14	5 - 7	Primary hyperparathyroidism is probably most often discovered after a routine blood test because the condition is not well enough	Thank you for your comment. We anticipate that these guidelines will raise awareness of PHPT.

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				known and therefore calcium levels are not tested often enough by GPs when symptoms do occur. Perhaps guidelines should suggest further awareness of this disease in GP surgeries.	
Hyperparathyroid UK Action 4 Change	Guideline	14	6 - 7	*In addition, the committee noted that PHPT is most often discovered after a routine blood test that shows a raised **serum calcium** level.* This is inconsistent with page 3, lines 4-5: *Measure albumin-adjusted serum calcium for people with any of the 6 following features, which might indicate primary hyperparathyroidism.*	Thank you for your comment. We have edited this so that is now reads albumin-adjusted serum calcium.
Hyperparathyroid UK Action 4 Change	Guideline	14	8 - 13	I believe this apparent lack of evidence to be due to the fact we are one of very few countries in the world, if not the only one, who insist on albumin-adjusted calcium levels. How can UK research be compared with international research if this is indeed the case? Or is it actually the case that serum calcium levels are quoted in UK medical research papers, but albumin-adjusted calcium levels are the only ones to be considered when dealing with actual patients? And not forgetting of course; patients with high albumin levels will then have their serum calcium levels adjusted downwards and be told they cannot have a PHPT problem because: 'When we adjust your serum calcium measurement downwards for your high albumin level, your adjusted calcium level is within the normal range so we estimate you don't have PHPT' This can and does lead to misdiagnosis.	Thank you for your comment. The committee was confident to recommend this test as adjusted serum calcium has physiological importance. The biological effects of calcium are mediated by free calcium that is not bound to albumin and other proteins. In clinical practice an adjustment is made for serum albumin, which is the most significant protein that calcium binds to. When calcium is bound to this protein, it does not have biological activity. It is the free and metabolically available serum calcium that has biological, physiological and clinical effects.

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Hyperparathyroid UK Action 4 Change	Guideline	14	8 - 13	When **Dr R B Payne** developed his **formula for adjusting serum calcium for albumin**, he was working with very ill patients with low albumin levels. As I understand it, he didn't wish to treat them unnecessarily for hypOcalcaemia, so decided to adjust their serum calcium measurements *upwards* to take account of the calcium bound by what little albumin they had. But he actually stated in his work that one needed to be very careful when using his formula in reverse, i.e. adjusting *downwards* the serum calcium levels of patients with *higher* albumin levels A French paper from 2009 (Ann Biol Clin, vol 67, no 4, juillet-aout 2009) by X. Parent, C Spielman and A-M Hanser with the title Calcemie "corrigee": sous-estimation du statut calcique des patients sans hypoalbuminemie and des patients hypercalcemiques, translated as "Corrected" calcium: calcium status underestimation in non-hypoalbuminemic patients and in hypercalcemic patients, reports (in rather poorly translated English) that their results in this regard: *"agree with Payne's recommandations (sic) for the use of his adjustment formula: the clinically justified adjustment of a low calcemia due to an hypoalbuminemia should not be extended to other situations, particularly when albumin is increased."* It would appear that above a certain albumin level Payne's formula does not work correctly.	Thank you for your comment. What formula is used is determined locally and was not prioritised for a review question by the committee.

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				Indeed, some laboratories do not correct serum calcium measurements when the albumin is above a certain level, but this is not consistent nationally and, until it is, PHPT patients with high albumin levels will see their serum calcium measurements routinely adjusted downwards – when there is in fact an argument, as put forward by the above French paper, such levels should in fact be adjusted *upwards,* to account for a larger amount of calcium being bound by the larger amount of albumin in their blood. Another variable is the **use of a tourniquet** at blood draw. I have often been told that blood cannot be drawn without a tourniquet, which could indicate that tourniquet use is for the benefit of phlebotomy staff, rather than in the interest of obtaining a correct calcium result for the patient. "We have to get the blood out of you somehow" has been a frequent comment to me. Until it is made mandatory to **release the tourniquet as soon as blood flow is achieved**, it will always be possible that some patients' protein levels, and therefore albumin readings, will have been adversely affected by prolonged tourniquet use, which will affect their calculated albumin-adjusted calcium levels. The measurement of **ionised calcium** levels would perhaps give a truer reading of the patient's situation, and adjustment/correction of serum calcium measurements would seem to be an inadequate construct to try and reproduce cheaply what an ionised calcium reading would indicate.	

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Hyperparathyroid UK Action 4 Change	Guideline	14	12	This sentence needs to be amended to '*making the handling of ionised calcium measurement unreliable at certain facilities.*	Thank you for your comment. It is point-of-care testing that is unreliable not the facilities.
Hyperparathyroid UK Action 4 Change	Guideline	14	13	There is the same issue for PTH, the samples degrade very quickly if not chilled, or in the correct tube with the potential to produce a lower PTH reading. The handling of these samples needs to be agreed and standardised in all labs.	Thank you for your comment. As PTH is a relatively unstable element it is important that it is collected according to the relevant laboratory collection protocols. The method of collection was not identified as a topic for a review question by the committee. We have highlighted this topic with the surveillance review team so that they can search for evidence when it is published. This will be used to inform any update of this guideline. The committee were aware that most laboratories specify EDTA blood collection tubes. However specifying the anticoagulant is not possible in the absence of a review question on this topic. We have added this detail the committee discussion of the evidence.
Hyperparathyroid UK Action 4 Change	Guideline	14	14	This sentence ought to be considered and referred to in your recommendations for surgical referral and prescription of cinacalcet being limited to 2.85, as well as your recommendation in Table 1 when advising to only monitor blood levels only at 3 months after a failed parathyroidectomy. Levels can fluctuate from one week to another or as we have seen from one day to another.	Thank you for your comment. The committee recognises that there is some fluctuation in serum calcium (and also in the precision of the assays), and we therefore recommend repeated tests.
Hyperparathyroid UK Action 4 Change	Guideline	14	14	This extra step is time wasting and may result in patients not having the second test and in addition it is an extra step for our already time pressured GPs time which could be used elsewhere. If symptoms are there, including	Thank you for your comment. We do recommend that calcium should be taken at the same time as PTH (recommendation 1.1.6). The committee agreed that measuring vitamin D and correcting any deficiency is essential in diagnosing and

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				those such as fatigue and depression a blood test for calcium, PTH and Vitamin D from the same blood draw should be done. With careful handling of the PTH to avoid sample degradation.	treating people with primary hyperparathyroidism, but noted that correcting a deficiency does not need to precede the diagnosis. The committee discussed that for some primary care providers, vitamin D testing is not universally available. They considered that measuring and correcting vitamin D levels before the diagnosis may slow down referrals from primary care, and hence agreed that this test should be performed in secondary care to facilitate a more timely diagnosis. The committee discussed that vitamin D status can affect the interpretation of the urinary calcium test, hence in people who are vitamin D deficient, the specialist should interpret the urine calcium with caution. Untreated vitamin D deficiency may cause low urine calcium excretion. Correcting any deficiency may reveal normal or even elevated urine calcium excretion. However, the likelihood of a urine calcium result being low is highly unlikely. If this unlikely result is found, it is entirely appropriate to make sure that any vitamin D deficiency has been corrected. If the vitamin D deficiency has been corrected and the urine calcium is low, the diagnosis is unlikely to be primary hyperparathyroidism. As the likelihood of urine calcium being low even in vitamin D deficiency is highly unlikely, the committee did not make this a major feature of the diagnostic algorithm but when urine calcium is low, rarely, there is a major focus on ensuring vitamin D repletion. We have edited the committee's discussion of the evidence in evidence report B to include this detail. As PTH is a relatively unstable element it is important that it is collected according to the relevant laboratory collection protocols.

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					The method of collection was not identified as a topic for a review question by the committee. We have highlighted this topic with the surveillance review team so that they can search for evidence when it is published. This will be used to inform any update of this guideline. The committee were aware that most laboratories specify EDTA blood collection tubes. However specifying the anticoagulant is not possible in the absence of a review question on this topic. We have added this detail the committee discussion of the evidence.
Hyperparathyroid UK Action 4 Change	Guideline	14	14	If the Committee noted a person's serum calcium levels can vary then surely, they must recognise that calcium levels can go down as well as up or stay the same yet a patient can still be suffering from hyperparathyroidism if their PTH levels continue to remain high.	Thank you for your comment. We recommend repeat calcium testing.
Hyperparathyroid UK Action 4 Change	Guideline	14	14 - 20	We are very concerned that the cost of a parathyroid hormone test is mentioned several times, yet no recommendation or strict rule of how to test IPTH. We believe there are a vast amount of PTH tests that are a waste of funds based on the misunderstanding by many pathology departments of how to correctly test PTH in order to provide a more assured accuracy. There are recommendations here, to not routinely testing PTH but no mention that if not tested correctly, or with vitamin D at the first test in the same blood draw, then for those with a vitamin D deficiency, or those with normohormonal PHPT or those on estrogen therapy or with unregulated glycaemic index,	Thank you for your comment. As PTH is a relatively unstable element it is important that the blood test is taken according to the relevant laboratory collection protocols. The method of collection was not identified as a topic for a review question by the committee. We have highlighted this topic with the surveillance review team so that they can search for evidence when it is published. This will be used to inform any update of this guideline. The committee were aware that most laboratories specify EDTA blood collection tubes. However specifying the anticoagulant is not possible in the absence of a review question on this topic. We have added this detail the committee's discussion

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				the whole test becomes useless. Tests then often have to be repeated. It is not the fault of the patient if Pathologists are responsible for incorrect testing methods which may be placing this restriction due to cost. It makes more sense to us that the test should be correctly tested the first time which will result in savings associated with PTH testing. Our organisation has conducted much research on this matter and are aware of at least 9 NHS trusts covering large areas who clearly do not test PTH accurately, use the wrong vials, and pay no attention to storage temperature. Some of them have been approached and refuse to consider our research based on the fact 'they have always don't it this way'. Unstable PTH testing equals unreliable results which can and does lead to misdiagnosis. This should be included in the guidelines.	of the evidence.
Hyperparathyroid UK Action 4 Change	Guideline	14	14 - 20	We are concerned the guideline committee accepts on line 14 above, calcium may fluctuate, but PTH does not fluctuate apparently based on cost. We have submitted very good reasons to include testing magnesium with PTH initially to check for a paradoxical block of PTH by hypomagnesemia which may be preventing a diagnosis for some. Correcting a magnesium deficiency would obviously require a further PTH test. We have grave concerns that due to errors in testing PTH, the opportunity to have repeat tests is being advised against when so many of us depend on accurate results for a diagnosis. If we were confident all testing centres were using the correct procedures of using a full	Thank you for your comment. Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function. This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects on PTH secretion or function in PHPT. We have added this to the committee's discussion of the evidence. As PTH is a relatively unstable element it is important that it is collected according to the relevant laboratory collection protocols.

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				EDTA vial, there may routinely be savings costs as once a diagnosis is confirmed, and a timely surgery referral is made, there may not be a need for repeat PTH tests until just before surgery unless a patients symptoms worsen. We have conducted much research of implementing this approach and would be willing to submit our experiences to the NICE shared learning database. Contact Sallie Powell	The method of collection was not identified as a topic for a review question by the committee. We have highlighted this topic with the surveillance review team so that they can search for evidence when it is published. This will be used to inform any update of this guideline. The committee were aware that most laboratories specify EDTA blood collection tubes. However specifying the anticoagulant is not possible in the absence of a review question on this topic. We have added this detail the committee's discussion of the evidence.
Hyperparathyroid UK Action 4 Change	Guideline	14	14 - 20	The cost of PTH testing may be high, but it is *essential* for diagnosis. These guidelines suggest that monitoring calcium alone can lead to a diagnosis, but PTH testing is essential, particularly for people with normocalcaemic hyperparathyroidism.	Thank you for your comment. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above. There are no substantive objective data on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B
Hyperparathyroid UK Action 4 Change	Guideline	14	14 - 20	The committee agree that serum calcium can be variable – how can a series of two measurements show the variability given that one may be 2.61and the next 2.49?	Thank you for your comment. These recommendations do not replace clinical judgement or preclude further calcium testing being carried out in the circumstances you describe.
Hyperparathyroid UK Action 4 Change	Guideline	14	15 - 16	One week apart (no need to delay diagnosis and prolong patients symptoms/ill health).	Thank you for your comment. The time interval between tests will vary on a case-by-case basis depending on the level of calcium and symptoms.
Hyperparathyroid UK Action 4 Change	Guideline	14	15 - 16	There is absolutely no need to wait any considerable time to take 2nd or even 3rd calcium tests. After an adjusted serum calcium result of 2.77 in July 2011, my hospital lab requested a repeat test. The result a week later was 2.81. My doctor thought for some reason it might be a lab error so requested a	Thank you for your comment. Under this guidance your GP would perform the PTH after the second calcium test and given the combination of results would then seek specialist advice.

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				further test the next day which came back at 2.91. 3 tests in 2 weeks, there was no doubt even though my PTH came back at below midpoint. I had Normohormonal Primary Hyperparathyroidism which represents according to this study 22.5 % of the parathyroid population. https://www.medscape.com/medline/abstract/27866715 Please be very aware of normohormonal primary hyperparathyroidism.	
Hyperparathyroid UK Action 4 Change	Guideline	14	21 - 23	I would advise also from personal experience; raising awareness that some people diagnosed with fibromyalgia may actually have primary hyperparathyroidism. There are many people in our organisation diagnosed with fibromyalgia before PHPT was eventually diagnosed. Please read this article. https://www.healthrising.org/blog/2014/05/08/alternate-diagnoses-fibromyalgia-hyperparathyroidism-treatable-condition/	Thank you for your comment. We have referred to two of the common symptoms that may be associated with PHPT. Fibromyalgia is one of many possible differential diagnoses and it is not possible to list the symptoms of all of them. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have amended recommendation 1.1.2 to be inclusive of all non-differentiated symptoms associated with PHPT. We now list the common symptoms in the section 'terms used in this guideline' and in the committee's discussion of the evidence in evidence report A to reflect those mentioned in your comment on the most common symptoms.
Hyperparathyroid UK Action 4 Change	Guideline	14	21 - 23	As already well established in other comments. Fatigue and depression are only a fraction of the symptoms caused by primary hyperparathyroidism. If you really want to raise awareness, you will consider our comments to amend this. Please see the General comment with link to symptoms from the fourth international endocrine workshop. There is hardly a lack of evidence available regarding the symptoms of primary hyperparathyroidism.	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted

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				It is unclear why you have chosen to ignore them.	serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	14	21 - 23	The NICE Clinical Knowledge Summary for hypercalcaemia lists a considerable number of clinical features of hypercalcaemia which are not listed within the guidelines. The guidelines should note that the suggested symptoms are not exhaustive and refer clinicians to the CKS by a hyperlink so that the full extent of clinical features of hypercalcaemia can be considered in deciding whether to measure albumin-adjusted serum calcium. https://cks.nice.org.uk/hypercalcaemia#!topicsummary	Thank you for your comment. The electronic pathway on the NICE website will link to the NICE CKS.
Hyperparathyroid UK Action 4 Change	Guideline	14	21 - 25	Calcium testing 'could' be considered for people with 'undifferentiated symptoms'. Guidelines should suggest that every person	Thank you for your comment. Recommendation 1.1.1 is based on symptoms with a strong association with PHPT.

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				presenting with ongoing fatigue or depression should have calcium and PTH tested before other medication is prescribed.	A consider recommendation (1.1.2) is made for other symptoms where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain. Given the symptoms you describe a GP following these recommendations would test for calcium.
Hyperparathyroid UK Action 4 Change	Guideline	14	23 - 25	There is complete certainty about the relationship between undifferentiated symptoms such as fatigue and depression and phpt. Perhaps the committee should read the recent research carried out by Hirotaka Ishii (Clinical Research fellow in ENT surgery at Taunton and Somerset NHS) earlier this year.	Thank you for your comment. We have made the committee aware of this research.
Hyperparathyroid UK Action 4 Change	Guideline	14	28	*The committee based their recommendations on the normal reference range for **serum***	Thank you for your comment. The recommendations are consistent with the paragraph you cite. We

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				calcium *as defined by the Association of Clinical Biochemistry, which is 2.2 to 2.6 mmol/litre and their own experience. They noted that most people with PHPT have a* ***serum calcium*** *above 2.6mmol/litre.* This is inconsistent with page 3, lines 4-5: *Measure albumin-adjusted serum calcium for people with any of the 6 following features, which might indicate primary hyperparathyroidism*	recommend PTH testing in people with an albumin-adjusted serum calcium of 2.6 mmol/litre or 2.5 mmol/litre with symptoms.
Hyperparathyroid UK Action 4 Change	Guideline	14	28	If the committee based their recommendation on the normal reference range for **serum calcium**, range of 2.2-2.6mmol/l, why did they then decide to use a patient's albumin-adjusted calcium levels as the benchmark for diagnosis/referral, when these vary greatly between individuals due to different albumin levels, and indeed will vary within the same individual due to fluctuations in their own albumin levels due to their level of hydration at blood draw, and extended use of a tourniquet?	Thank you for your comment. Screening calcium was not identified as a topic during the scope consultation. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. Including this in the future updates of this guideline may be possible if further evidence becomes available. Some cases of normocalcaemic PHPT are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Guideline	14	28	As not all laboratories quote the same range for albumin-adjusted calcium, so there will be no consistency here. It is not appropriate to	Thank you for your comment. The committee agreed that not all laboratories use exactly the same adjustment for serum albumin. There

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				apply the normal reference range for **serum calcium** as defined by the Association of Clinical Biochemistry to a patient's **albumin-adjusted calcium levels.**	may be minor differences but it is also important to recognise that the reliability of repeat calcium measurements is also not 100%. In other words, there is inherent error within measurement of any biological variable. By repeating the measurement on two occasions, the committee were confident that those patients with primary hyperparathyroidism and hypercalcaemia will be detected with the current guideline, more readily than in previous international guidelines as the threshold for definition of hypercalcaemia in this guideline is lower than has ever been quoted before. To make the guideline workable also, there needs to be a clear threshold that is based on accepted reference ranges.
Hyperparathyroid UK Action 4 Change	Guideline	15	4	The relationship between Calcium and PTH is key; it needs to see-saw appropriately. Graphing blood test results can help make that clearer.	Thank you for your comment. The committee agree that graphing results can sometimes be helpful.
Hyperparathyroid UK Action 4 Change	Guideline	15	4	It is a real concern that that there is only a single mention of normocalcaemia within the entire guideline. For a condition that is not very well understood even by medical specialists i.e. endocrinologists. There is no mention or reference to the existence of normocalcaemic hyperparathyroidism and how it should be dealt with. If the guideline does recognise normocalcaemia then why has it set a threshold of 2.5 mmol/litre? Surely normal means anywhere in the normal range of 2.2 to 2.6 mmol/litre.	Thank you for your comment. The committee's definition of PHPT that is used in the guideline does not preclude people with normal calcium. Some cases of normocalcaemic PHPT are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Guideline	15	8	Correct handling of PTH samples is needed to avoid degradation of samples and false low level results being provided.	Thank you for your comment. As PTH is a relatively unstable element it is important that it is taken according to the relevant laboratory collection protocols. However, it is not within the scope of this guideline to

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					specify local laboratory collection protocols. We have added this detail the committee's discussion of the evidence. The committee are aware that most laboratories do specify using an EDTA blood collection tube. However specifying the anticoagulant used was not raised during the scoping process of this guideline.
Hyperparathyroid UK Action 4 Change	Guideline	15	11 - 13	According to the Association of Clinical Biochemistry (whose recommendation for calcium levels the committee accept on p14 of the guidelines) PTH shows some diurnal variation and the ACB recommend that samples are obtained in the morning, preferably after an overnight fast. There is need for clarity here as some labs are recommending fasting and others are not. If taken with calcium which is not a fasting test, then a non-fasting PTH is practical also. I had tests at two different hospitals only to find out later their protocol was different. This needs to be regulated and made very clear. Non clarity can affect results	Thank you for your comment. We specify that the sample can be random.
Hyperparathyroid UK Action 4 Change	Guideline	15	16	If the guideline does recognise normocalcaemic primary hyperparathyroidism, then why has it set a threshold of 2.5 mmol/L? Normal means anywhere in the normal range of 2.2 to 2.6 mmol/L.	Thank you for your comment. In the absence of evidence the committee focused on the upper point for the threshold of the reference range of calcium. The committee considered that it would be highly unlikely to be cost effective to recommend PTH testing in everyone with a calcium 2.2–2.5 mmol/litre as the number of people who would be diagnosed with PTHT would be so small.
Hyperparathyroid UK Action 4 Change	Guideline	15	16 - 17	*This sentence is incomplete and should include ' if satisfied accurate and correct testing conditions were applied (EDTA) and the patient's mineral levels have also been noted to assist with referral for possible implications of a lower PTH level due to*	Thank you for your comment. The purpose of this section is to explain the rationale behind the recommendations. We have not made recommendations on EDTA or hypomagnesemia. We do discuss these in the discussion of the evidence in evidence report B.

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				hypomagnesemia or higher PTH due to vitamin D deficiency recorded.	
Hyperparathyroid UK Action 4 Change	Guideline	15	16 - 17	*'They also agreed that there is no benefit in repeating the PTH measurement before referral'.* This is understandable to an extent, as a diagnosis has been made, but it should take into consideration the waiting time for the referral as often this wait can be 6 -9 months in some areas, during which time symptoms can become worse, in which case a repeat calcium, PTH, vitamin D and magnesium ought to be taken to determine a biochemical cause of the worsening symptoms. An example is vitamin D deficiency over winter months can have an effect on PTH levels, or hypomagnesemia from vitamin D supplements can affect both vitamin D and PTH Levels. One recommendation is not suitable for all, each person needs to be monitored as needed as individuals.	Thank you for your comment. The recommendations do not preclude advice being sought by a GP whilst waiting for a referral. In the committee's knowledge and experience it is important to conduct a second PTH in secondary care when performing other tests to establish the diagnosis of PHPT. The committee therefore agreed that measuring vitamin D and correcting any deficiency is essential in diagnosing and treating people with primary hyperparathyroidism, but noted that correcting a deficiency does not need to precede the diagnosis. The committee discussed that for some primary care providers, vitamin D testing is not universally available. They considered that measuring and correcting vitamin D levels before the diagnosis may slow down referrals from primary care, and hence agreed that this test should be performed in secondary care to facilitate a more timely diagnosis. The committee discussed that vitamin D can affect the interpretation of the urinary calcium test, hence in people who are vitamin D deficient, the specialist should interpret the urine calcium with caution. However the likelihood of a urine calcium result being low is highly unlikely and the committee agreed this should not be a major feature of the diagnostic algorithm but when urine calcium is low, rarely, there is a major focus on ensuring vitamin D repletion. We have edited the committee's discussion of the evidence in evidence report B. Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function.

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					This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects on PTH secretion or function in PHPT. We have added this to the committee's discussion of the evidence.
Hyperparathyroid UK Action 4 Change	Guideline	15	17	This sentence ends; 'before referral'. It needs to include referral to either endocrinologist or surgeon.	Thank you for your comment. We have edited this to better reflect the recommendation which is to seek advice from a specialist with expertise in PHPT.
Hyperparathyroid UK Action 4 Change	Guideline	15	18	*'The committee noted that PTH levels can vary widely from one individual to another, and that there is uncertainty about the level of PTH at which primary hyperparathyroidism can be ruled out'*. Where is the evidence to support this statement? It reads as unsatisfactory that the committee are unable or unwilling to comment on set points between different ranges when members of our group, who would be considered as laypersons have become quite efficient at determining satisfactory or unsatisfactory results from different ranges, at a glance, when compared to a corresponding serum adjusted calcium, with or without brain fog. https://www.sciencedirect.com/science/article/pii/S0039606011005253 This study; 'The phenotype of primary hyperparathyroidism with normal parathyroid hormone levels: How low can parathyroid hormone go?' may help you with this statement. To us, hypercalcemia, symptoms of primary hyperparathyroidism and	Thank you for your comment. We refer to the reference range for PTH in the recommendations (1.1.8 and 1.1.9) rather than specific set-points as the former varies between laboratories.

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				a detectable parathyroid hormone level is more than enough to request a location scan, dexa scan, and a referral to an experienced surgeon.	
Hyperparathyroid UK Action 4 Change	Guideline	15	19	The uncertainty about the level of PTH at which primary hyperparathyroidism can be ruled out should take into consideration the patients symptoms, the corresponding level of calcium and other minerals, testing conditions, dexa bone scan and whether the patient has a history of previous primary hyperparathyroidism. https://link.springer.com/article/10.1007/s00268-016-3716-6 The diagnosis of primary hyperparathyroidism (1°HP) has become more complex, as fewer patients present with classic phenotype of concomitant elevation of calcium and parathyroid hormone (PTH). In addition, the distinction between normal versus abnormal patients is challenging, with an increasing number of patients with 1°HP, who have calcium and/or PTH values within the "reference" range. Patients with "inappropriately" elevated PTH values relative to their serum calcium are considered to have 1°HP.	Thank you for your comment. The committee agreed that there is uncertainty about the level of PTH at which primary Hyperparathyroidism can be excluded, which is why the guideline encouraged a GP to seek specialist opinion in recommendation 1.1.8 on the basis of both calcium and PTH levels. In the knowledge and experience of the committee the levels of other minerals and testing conditions do not make an important contribution to the diagnosis in primary care. The specialist may well take such factors into account, but there is not the available evidence base to enable us to make firm recommendations on such topics. The committee sought to not overburden the GP with unnecessary investigations prior to referral which might delay appropriate treatment.
Hyperparathyroid UK Action 4 Change	Guideline	15	24 - 26	*'The committee recognised that repeat calcium testing will reduce the number of unnecessary PTH tests.'* Why? Once maybe, but we have already established the parathyroid glands have one job; to regulate calcium. To test one without the other provides an inconclusive picture, so why have to test calcium alone again, once an elevated result has been found?	Thank you for your comment. The committee considered it important to repeat an albumin-adjusted serum calcium test to confirm that an initial elevation in serum calcium level was repeated prior to PTH testing due to the intra-individual variability in calcium levels. As the cost of a clinical biochemistry test (including that for calcium) is relatively low, the committee considered it important that there is confirmation of hypercalcaemia.

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Hyperparathyroid UK Action 4 Change	Guideline	15 - 16	32 - 3	*'If PTH is below the midpoint but albumin-adjusted serum calcium is raised, specialist advice should be sought because there are a small number of people who have primary hyperparathyroidism with a low PTH'* 22.5% of the parathyroid population is the recorded number of people with Normohormonal Primary Hyperparathyroidism. Please do not exclude us from this guideline as our symptoms are just as severe and potentially life shortening as everybody else with Primary Hyperparathyroidism. Please view these slides prepared by Dr Babak Larian, Clinical Chief of Head and Neck Surgery of Cedars-Sinai Medical Centre, called 'The many faces f Hyperparathyroidism'. They are very easy to understand and will help the committee to understand what we, the patients already know about our disease. Slides 29 and 41-44 are very helpful regarding normohormonal primary hyperparathyroidism. https://www.slideshare.net/BabakLarian/the-many-faces-of-hyperparathyroidism-advances-in-treatment	Thank you for your comment. The committee's definition of PHPT that is used in the guideline does not preclude people with PTH below mid-range being diagnosed with PHPT. Recommendation 1.1.8 – 'Seek advice from a specialist with expertise in primary hyperparathyroidism if their PTH measurement is below the midpoint of the reference range with a concurrent albumin-adjusted serum calcium level of 2.6 mmol/litre or above' - includes people with normohormonal PHPT. In this case the GP would perform the PTH test after the second calcium test and given the combination of results would then seek specialist advice.
Hyperparathyroid UK Action 4 Change	Guideline	16	1 - 3	The distinct entity of Normohormonal PHPT appears to be briefly referred to here, but needs to be mentioned by name, as health professionals may read the guidelines but perhaps not those pages explaining the committee's reasoning behind them, which contains the indirect mention of Normohormonal PHPT. Please read this paper: **Normohormonal primary**	Thank you for your comment. The committee's definition of PHPT that is used in the guideline does not preclude people with PTH below mid-range being diagnosed with PHPT. Recommendation 1.1.8 – 'Seek advice from a specialist with expertise in primary hyperparathyroidism if their PTH is below the midpoint of the reference range with a concurrent albumin-

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				hyperparathyroidism is a distinct form of primary hyperparathyroidism https://www.sciencedirect.com/science/article/pii/S0039606016305190	adjusted serum calcium level of 2.6 mmol/litre or above' - includes people with normohormonal PHPT. In this case the GP would perform the PTH test after the second calcium test and given the combination of results would then seek specialist advice.
Hyperparathyroid UK Action 4 Change	Guideline	16	1 - 3	'The parathyroid glands control the calcium in the blood. If the calcium in the blood is ever high, "normal" parathyroid glands would sense the high calcium and turn themselves off--and the PTH level would be near zero. Thus, if the PTH level is in the normal range when the calcium is high, then there is something wrong with the parathyroid glands, and one (or more) of them has lost their ability to 'turn off' and it is stuck in the 'on' position. This bad parathyroid gland should be removed. Think of it this way... a "normal" parathyroid hormone level is only normal if your calcium is normal. If your calcium is high, then a "correct" parathyroid hormone would be very low... if your parathyroid glands are normal. If not, then it is the parathyroid glands that are CAUSING the calcium to go high' an extract from: https://www.parathyroid.com/diagnosis.htm?fbclid=IwAR1BlMAckTekqdSJOcXhry5z821dz-SDp_trnbz58R3xXtG3lCeHqPJl0GY	Thank you for your comment. The committee agreed with your comment and this is why we recommend in recommendation 1.1.8 that specialist advice should be sought if PTH is below the mid-point of the reference range if the serum calcium is elevated.
Hyperparathyroid UK Action 4 Change	Guideline	16	1 - 3	Please read this 2017 article based on a population study of 1753 people with clinically proven primary hyperparathyroidism. We believe this guideline would greatly benefit from adapting this information as an introduction on page 1. Patients with an awareness of PHPT are aware of it, and we need our doctors to be aware in order to help	Thank you for your comment. The committee's definition of PHPT that is used in the guideline does not preclude people with normal calcium or with mid-range PTH being diagnosed with PHPT.

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				us on the right path to surgery. *The diagnosis of primary hyperparathyroidism (1°HP) has become more complex, as fewer patients present with classic phenotype of concomitant elevation of calcium and parathyroid hormone (PTH). In addition, the distinction between normal versus abnormal patients is challenging, with an increasing number of patients with 1°HP, who have calcium and/or PTH values within the "reference" range. Patients with "inappropriately" elevated PTH values relative to their serum calcium are considered to have 1°HP.* https://link.springer.com/article/10.1007/s00268-016-3716-6	
Hyperparathyroid UK Action 4 Change	Guideline	16	1 - 3	Firstly, this should read "there *is* a small number" to be grammatically correct. Secondly, if this refers to normohormonal primary hyperparathyroidism then this condition should be named as such, so that medical professionals who wish to research it further have the correct search term to use.	Thank you for your comment. We have amended this. The committee did not define normohormonal primary hyperparathyroidism as this term is not used by health professionals, but the definition of PHPT in this guideline does not preclude people with PTH below mid-range being diagnosed with PHPT.
Hyperparathyroid UK Action 4 Change	Guideline	16	1 - 3	Your guideline on hypomagnesemia does not mention its effect on parathyroid hormone levels and maybe needs to be reviewed accordingly. This is from Oxford university Hospitals. Hypercalcemia can cause hypomagnesemia which in turn can lower PTH levels so why is it not recommended to be tested in this guideline? http://nssg.oxford-haematology.org.uk/oxford/clinical-care/H-95-guidelines-for-management-of-	Thank you for your comment. The committee's definition of PHPT that is used in the guideline does not preclude people with PTH below mid-range being diagnosed with PHPT. Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function. This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects

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				hypomagnesaemia-in-adult-clinical-haematology.pdf	on PTH secretion or function in PHPT. We have added this to the committee's discussion of the evidence.
Hyperparathyroid UK Action 4 Change	Guideline	16	12	Whilst any one of three tests can be used to exclude FHH, no one particular test has been recommended as perhaps the 'Gold' standard. Also, by not recommending or proposing thresholds for these measures, how is it possible to confirm the exclusion of FHH? How will it be ensured that patients across the UK are treated in a consistent manner when ruling out FHH?	Thank you for your comment. The diagnosis of FHH was not prioritised during the scoping process of this guideline. We looked at evidence for the screening tests but only identified one study. All 3 tests were very similar in terms of diagnostic accuracy. We were therefore unable to recommend one test over another. Cut-offs for these tests are determined locally.
Hyperparathyroid UK Action 4 Change	Guideline	16	15 - 16	*Based on the evidence, they agreed that any one of 3 tests to 16 measure urine calcium excretion could be used.* Please name the 3 tests.	Thank you for your comment. The purpose of this section is to provide explanation of the recommendations and not repeat them.
Hyperparathyroid UK Action 4 Change	Guideline	17	8 - 9	As previous suggestions these 3 are not the main symptoms. List actual most prolific symptoms. In my mind excessive thirst and frequent urination = Diabetes! I am sure anybody with diabetes will have thought the same.	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion of the evidence in evidence report A. The guideline recommends how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test where those

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					symptoms are present?. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Guideline	17	8 - 9	I really believe listing only these symptoms will lead to delays in diagnosis for those of us who also have diabetes. My diagnosis was delayed by several years as my endocrinologist believed my insatiable thirst and prolific polyuria was diabetes related despite being diet controlled. It is worth noting also that poorly controlled glycaemic index can negatively impact PTH, so blood sugar levels and type 2 diabetes should be ruled out early on or considered in relation to assessing PTH levels with high normal or elevated calcium. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2362.1983.tb00116.x	Thank you for your comment. We anticipate that these recommendations will raise awareness of PHPT. The committee are unaware of a relationship between a poorly controlled glycaemic index an PTH. We have made the committee aware of the reference.
Hyperparathyroid UK Action 4 Change	Guideline	17	8 - 9	Again, the symptoms of fatigue, anxiety, depression and atrial fibrillation should be included here.	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have

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					amended the list of symptoms in the rationale and committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience.
Hyperparathyroid UK Action 4 Change	Guideline	17	10-13	*'Therefore it could lead to savings' A*nd, of course reduce long term sickness, absences from work and attendance at GP surgeries and endless hospital consultations per patient.	Thank you for your comment. This has been edited to say the following: "However, the committee considered that if such testing helps to diagnose and treat primary hyperparathyroidism sooner then this could reduce the number of fractures or renal stones due to primary hyperparathyroidism, *as well as frequent GP and hospital appointments for chronic non-differentiated symptoms*, and therefore it could lead to savings."
Hyperparathyroid UK Action 4 Change	Guideline	17	12	This disease is progressive, so delays in treatment frequently incur extra workload and costs to the NHS. One example of this is that many in our group who have had treatment delayed suffer greatly from renal problems. The number of admissions to hospital for stents, kidney stones etc. is distressing to the patients and both costly and disruptive to the NHS. The sooner hyperparathyroidism is treated the lower the risk of problems coming from it.	Thank you for your comment. The intention of the guideline is to ensure prompt diagnosis and treatment.
Hyperparathyroid UK Action 4 Change	Guideline	17	24 - 25	We are astonished there was no evidence, we are swamped with evidence as are all departments in every hospital who see patients with primary hyperparathyroidism. Every symptomatic patient desperate for surgery, waiting months, years and decades are all the evidence you need of non-surgical treatment. We advise and are happy to help with devising	Thank you for your comment. The guideline was developed in accordance with the NICE guidelines manual (2014). NICE guideline development methods processes have been followed throughout the development of this guideline. Evidence from randomised controlled trials (RCT) has been prioritised, as these are viewed as of the highest quality for questions on interventions due

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				a much needed post-operative feedback questionnaire to prove the difference surgery makes to people who have suffered whilst waiting for surgery.	to their rigorous design that makes them the least susceptible to bias. This has been done to ensure the resulting recommendations are based on the best available evidence. Where no RCT evidence has been available, the committee has considered looking at non-randomised evidence/lower quality evidence a priori on a question-by-question basis. In areas where no such clinical evidence was identified, the committee used their collective experience to make consensus recommendations. The committee also identified areas where evidence to answer their review questions was lacking and have used this information to formulate recommendations for future research. The committee was comprised of people with knowledge and experience of primary hyperparathyroidism. How the committee made the recommendations is captured in the committee's discussion of the evidence in the evidence reports and in the rationale and impact sections of the short guideline. We expect that the guideline will increase awareness of primary hyperparathyroidism including the wide range of symptoms that people may experience. We have sought to make clear recommendations on when advice from a specialist should be sought. All people with the condition should now be considered for referral to surgery. The guideline should reduce variation in practice and improve outcomes for people affected by the condition.
Hyperparathyroid UK Action 4 Change	Guideline	17	24 - 27	If GP'S, Psychiatrist's and Endocrinologists don't understand the link of symptoms to PHPT, diagnosis will continue to be missed. Given the numbers of people with PHPT suffering from mental health symptoms for example, we believe they should be mentioned	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have amended recommendation 1.1.2 to be inclusive of all non-differentiated symptoms associated with PHPT. We now list the common

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				in this guideline. Many are prescribed anti-depressant or other mental health drugs. Some are treated with ECT. Some including myself are placed in Mental Health hospitals. I am struggling to deal with this post-op knowing primary hyperparathyroidism was the cause. Treating symptoms and not the cause is a major contender for misdiagnosis with this disease, further adding to the unnecessary financial costs to the NHS and the cost of the continuing progression of the disease to the person, including the impact on their quality of life. It is important that there is a clear link to symptoms and diagnostic testing of albumin-adjusted serum calcium. This section needs to address these issues. There is plenty of evidence, it just needs somebody to join the dots and make the connection.	symptoms in the section 'terms used in this guideline' and in the committee's discussion of the evidence in evidence report A to reflect those mentioned in your comment on the most common symptoms.
Hyperparathyroid UK Action 4 Change	Guideline	18	1 - 2	Guidelines should suggest that patients be made **clearly aware** that calcimimetics have no curative benefit and should not be used long term. Patients should be made fully aware of the possible side effects of using calcimimetics.	Thank you for your comment. Recommendations 1.5.2 and 1.5.3 cover the points you raise and we have discussed this in the rationale and impact section.
Hyperparathyroid UK Action 4 Change	Guideline	18	18	*Indications for surgery are in line with current practice* is just not a true reflection of what is happening in some areas and even within some hospitals where one surgeon will refuse surgery on the basis of calcium levels but offer the same surgery at the same hospital with the same levels if a person can afford to pay privately. Yes, in some areas your recommendations are in line with current practice, which in the long term is costing the NHS much more, it's quite a simple equation;	Thank you for your comment. In the knowledge and experience of the committee the indications for surgery are current practice with the exception that we recommend that people without the symptoms specified are still considered for referral.

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				parathyroidectomy or treatment for complications and consequences of a progressive disease for the entirety of ones life.	
Hyperparathyroid UK Action 4 Change	Guideline	18	19	*'And are not expected to have a substantial resource impact'* The resource impact of curing or not curing sick people can only be beneficial short and long term to both patients and the NHS. Surely? Surgery will cure. Monitoring will not.	Thank you for your comment. When mentioning resource impact in the guideline we are referring to the potential impact of implementing the recommendations compared to what already occurs in current practice. The text has been edited to clarify that the committee considered that the recommendations made for indications for surgery are broadly in line with current practice. The committee is uncertain how many additional surgeries will be performed as a result of the recommendation to consider surgery for people without with primary hyperparathyroidism who do not have symptoms or signs, but the committee do not anticipate there will be a significant increase in the number of referrals for surgery to result in a substantial increase in resource for the NHS. The impact on cost of undertaking surgery compared to monitoring was discussed by the committee which is detailed in section 1.8.2 in evidence review C.
Hyperparathyroid UK Action 4 Change	Guideline	18	19 - 23	Any additional costs would be offset by the savings made in wasted GP appointments, scans for other conditions, and long term deterioration into osteoporosis, and other consequences of untreated primary hyperparathyroidism.	Thank you for your comment. We expect that implementation of the guideline will ensure prompt diagnosis and treatment.
Hyperparathyroid UK Action 4 Change	Guideline	19	12 - 17	*However, they noted that the accuracy of ultrasound depends on the expertise of the person performing it and ideally should be performed by a head and neck radiologist. They therefore allowed for sestamibi to be used if the expertise is not available to perform*	Thank you for your comment. The committee discussed that although ultrasound is good for identifying glands in the neck, it cannot identify if the diseased glands are located either deep in the neck or in the chest. Sestamibi/4DCT gives functional information about dominant hyper-functioning regions

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				ultrasound. The accuracy of the ultrasound also very much depends on the possibility of ectopic glands which must be added here. https://www.ncbi.nlm.nih.gov/pubmed/22968537?fbclid=IwAR2lZLr8RWbevss5XDzsi__iIKMkepiC9v0HXLiAb2GvnpbEKz1IntVVoX4	in the neck. They also noted that sestamibi/4DCT has the ability to show ectopic adenomas in the neck. The advantages of sestamibi scans/4DCT are their ability to evaluate for diseased glands outside of the neck at the same time. Hence when there is a fifth parathyroid gland in an ectopic position; functional imaging will pick it up but not anatomical imaging. The committee discussed the value of 4DCT but due to lack of evidence did not make a specific recommendation for this technique.
Hyperparathyroid UK Action 4 Change	Guideline	19	19 - 21	It should also be recommended for localisation of persisting parathyroid tissue in patients with persistent or recurrent disease. https://www.insideradiology.com.au/parathyroid-mibi-scan-hp/?fbclid=IwAR1niTH9pduNbjUbCN3hZsub33s9nLpveCON8IE7tHlI2xGgaL6M6HOJ46Q	Thank you for your comment. The committee discussed various pre-operative localisation techniques including sestamibi scanning, ultrasound of the neck, SPECT/CT, 4DCT, venous sampling and PET scanning options in people with persistent or recurrent disease in those who have had previous surgery. Due to lack of sufficient evidence for any technique, the committee did not make a specific recommendation for the type of pre-localisation technique. The committee considered that further localisation for patients with failed surgery should take place at a specialised centre with expertise and should be the result of a decision made by a multi-disciplinary team at the centre in conjunction with the patient. The reference provided is from an information site and is not considered as evidence in the NICE guideline process. NICE guidelines prioritise evidence from randomised controlled trials, as these are viewed as of the highest quality for questions on interventions and diagnosis due to their rigorous design that makes them the least susceptible to bias. Where no RCT evidence was available or when RCTs are not the most appropriate study design to answer the question, the

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					committee considered to look at non- randomised evidence/lower quality evidence a priori on a question-by- question basis. The details of this can be found in the protocols in appendix A of the evidence reports.
Hyperparathyroid UK Action 4 Change	Guideline	19	29 - 30	You may be basing this recommendation of focused parathyroidectomy on the certainty of scans, and/or ideal location of parathyroid adenomas which we know from experience is often not the case therefore a focused parathyroidectomy is not always a shorter surgery time. The benefit of a smaller incision from our experience is more often considered to be preferable for the reason of healing purposes rather than cosmetic. To be rid of this disease is THE most important factor for anybody who has suffered from it.	Thank you for your comment. We do not preclude the practice of 4-gland exploration in people who have had preoperative imaging that shows a single adenoma in the neck. In recommendation 1.4.6 we now refer to what information should be provided to assist someone making a decision between 4-gland exploration and focused parathyroidectomy.
Hyperparathyroid UK Action 4 Change	Guideline	20	12 - 15	Technology is not available across all health boards	Thank you for your comment. The committee is confident that the technology to measure albumin-adjusted serum calcium levels and parathyroid hormone levels is available across England.
Hyperparathyroid UK Action 4 Change	Guideline	20	20	Calcium, PTH, magnesium and Vitamin D should be tested together to show the full picture. There have been a few people within our group whose numbers were not normal in the year post op.	Thank you for your comment. We do recommend that calcium should be taken at the same time as PTH (recommendation 1.1.6). The committee also agreed that measuring vitamin D and correcting any deficiency is essential in diagnosing and treating people with primary hyperparathyroidism, but noted that correcting a deficiency does not need to precede the diagnosis. The committee recognises the importance of correcting vitamin D deficiency, but for some primary care providers vitamin D testing is not available. This would slow down referrals from primary care, and can therefore be done in secondary care. The committee discussed that vitamin D status can affect the interpretation of the urinary calcium test, hence in people who are vitamin D deficient, the

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					specialist should interpret the urine calcium with caution. Untreated vitamin D deficiency may cause low urine calcium excretion. Correcting any deficiency may reveal normal or even elevated urine calcium excretion. However, the likelihood of a urine calcium result being low is highly unlikely. If this unlikely result is found, it is entirely appropriate to make sure that any vitamin D deficiency has been corrected. If the vitamin D deficiency has been corrected and the urine calcium is low, the diagnosis is unlikely to be primary hyperparathyroidism. As the likelihood of urine calcium being low even in vitamin D deficiency is highly unlikely, the committee did not make this a major feature of the diagnostic algorithm but when urine calcium is low, rarely, there is a major focus on ensuring vitamin D repletion. We have edited the committee's discussion of the evidence in evidence report B to include this detail. Very low serum magnesium can suppress PTH secretion and also cause resistance to PTH function. This can occur when magnesium is very low and will usually have presented via symptomatic hypomagnesaemia/hypocalcaemia. The committee does not recognise that mild reductions in serum magnesium have material or clinically relevant effects on PTH secretion or function in PHPT. We have added this to the committee's discussion of the evidence.
Hyperparathyroid UK Action 4 Change	Guideline	20	20 - 24	Should read: People who have had parathyroid surgery can be considered biochemically cured if their albumin-adjusted serum calcium and parathyroid hormone levels are within the reference range and in an	Thank you for your comment. The purpose of this section is to summarise the committee discussion of the evidence so that it is clear how the recommendations were formed.

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				appropriate inverse relationship with each other before discharge after surgery and 3-6 months after surgery.	
Hyperparathyroid UK Action 4 Change	Guideline	20	24	If all levels and symptoms are all good, this is fine, if not recommend 12 months after surgery. Some take longer to adjust than others	Thank you for your comment. The committee from their experience discussed that patients are considered to be biochemically cured if their PTH is in the reference range immediately following surgery and their serum calcium is within the reference range 3–6 months after surgery. The committee considered that the risk of recurrent disease following successful removal of a solitary adenoma is very low and that, after the 6-month check, it is sufficient for calcium to be checked as part of routine blood testing to a maximum of once a year. We have also amended recommendation 1.4.11 to monitor calcium no more frequently than once a year in people who have had successful surgery. The committee highlighted that for people with multiple gland disease there is a higher risk of recurrence than in those who had a single adenoma and in monitoring of such patients specialist opinion should be sought. However, the committee noted that the risk is still very low if the person has normal adjusted calcium at 3 to 6 months after surgery. The committee noted that persistently high calcium at 3–6 months would trigger testing of plasma PTH, i.e. calcium above 2.5 mmol/litre with symptoms /2.6 mmol/litre without symptoms, as per recommendations on monitoring (section 1.6 table 1).
Hyperparathyroid UK Action 4 Change	Guideline	21	1	The chances of surgery not being a success is more likely to be due to: • a failure to provide necessary tools	Thank you for your comment. The reasons for an unsuccessful surgery are numerous and can be complex. We therefore recommend a multidisciplinary

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				such as intra-operative monitoring of PTH and specialised scans such as 4D-CT or Choline Pet scans beforehand; • a failure to undertake a proper 4-gland assessment if agreed at the outset; or • The surgeon not being skilled or experienced enough to undertake the surgery in the first instance. Repeat surgery may not be common but due to underrepresentation on the NICE Committee of patients who have had repeat surgery you would be aware that in terms of numbers it cannot just be dismissed lightly as rare. Also one of your committee members performs more re-ops than most other UK surgeons, not always with a successful outcome.	team review in these circumstances. In the experience and knowledge of the committee as a collective repeat surgery is relatively uncommon. The committee made a research recommendation on this topic: 'What is the best and most cost-effective management strategy for people whose first surgery for primary hyperparathyroidism is not successful?'
Hyperparathyroid UK Action 4 Change	Guideline	21	2	We are concerned how little evidence there is on further surgical management after unsuccessful surgery. What is the reason for this? Is this due to lack of GP follow up/awareness? Less experienced surgeons prepared to re-operate for fear of failure? Are there higher numbers of uncured patients than currently recognised? More up to date research on current patients is needed. Could the number of uncured patients also be lower on the NHS due to the number of people forced to seek private surgery? The majority of surgeons operate privately and also work within the NHS. A lifetime of monitoring will not remove symptoms resulting in further GP visits, consultant appointments, scans and	Thank you for your comment. As in all guidelines, we have identified the evidence in accordance with the NICE guidelines manual (2014) that is of the lowest risk of bias. Identified studies were selected for inclusion based on criteria that have been agreed with the committee and pre-specified prior to systematic searching in each evidence review protocol, which serves to guide the search for the evidence and to eliminate any potential bias in the selection of the evidence that comes to be included in each evidence review. In the committee's expertise and knowledge the 'older' evidence was judged to be as applicable as the newer evidence. The extent to which decision making is then based on the evidence presented in the review depends on the quality assessment of the evidence and the

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				other treatments as the disease progresses.	committee's clinical expertise and knowledge. The committee agreed from their collective experience that input from a multidisciplinary team at a specialist centre should be sought, noting that repeat parathyroid surgery is relatively uncommon; failure rates are higher than in primary surgery and it carries a higher risk (recommendation 1.4.12). As there was lack of sufficient evidence in this area, they also made a recommendation for future research on management after unsuccessful primary surgery. We expect that the guideline will increase awareness of primary hyperparathyroidism including the wide range of symptoms that people may experience. We have sought to make clear recommendations on when advice from a specialist should be sought. All people with the condition should now be considered for referral to surgery. The guideline should reduce variation in practice and improve outcomes for people affected by the condition. Exploring reasons for cure rates in the NHS was not raised during the scoping process of this guideline.
Hyperparathyroid UK Action 4 Change	Guideline	21	5	Where are these specialist centres? Can they be named?	Thank you for your comment. NICE guidelines are unable to name specific centres.
Hyperparathyroid UK Action 4 Change	Guideline	21	5 - 7	Our stakeholder patient forum can attest to the fact that this bald assertion is not totally correct. A large number of our members have had to undergo repeat surgery which was ultimately successful. It might well carry a higher risk which is why they were forced to seek out highly experienced surgeons. The name of the new NHS initiative comes to mind in this connection which is Getting It Right First Time (!GIRFT):	Thank you for your comment. The page number does not match the comment but we assume you are referring to p20 line 24. As repeat surgery is associated with higher risks we recommend that people are referred for a multidisciplinary team review. The guideline is permissive of people having repeat surgery where indicated within the appropriate setting.

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				https://gettingitrightfirsttime.co.uk/	
Hyperparathyroid UK Action 4 Change	Guideline	21	22	A number of our group have been denied surgery as adenoma have not shown up on these scans, some have resorted to the private sector where adenomas have been found.	Thank you for your comment. We have now amended recommendation 1.4.4 to make it clearer. The committee acknowledged that preoperative imaging does not detect all adenomas, so 4-gland exploration should be offered if preoperative imaging does not identify an adenoma (recommendation 1.4.7).
Hyperparathyroid UK Action 4 Change	Guideline	21	22	I agree imaging is unreliable and needs to be done by experts. I had two ultrasounds, one done by a generalist who found nothing, another done by a Consultant who had done many scans for my surgeon, she found the adenoma. Scans help ease the search.	Thank you for your comment. The committee discussed that the accuracy of ultrasound depends on the expertise of the person performing it and ideally should be performed by a practitioner with expertise in head and neck imaging.
Hyperparathyroid UK Action 4 Change	Guideline	21	27	We are concerned the current practice for follow up after surgery is outdated/inadequate, therefore the draft, which also reflects this practice is showing a lack of research. If there is no change in these guidelines then patients will not see any benefits or improvements to their quality of life from just monitoring primary hyperparathyroidism which defeats your aims and ours.	Thank you for your comment. A search was conducted for assessing the optimum type and frequency of monitoring for people with PHPT. No evidence was identified for this review question. A second search of the original PHPT search was conducted to determine whether PHPT is associated with poor long-term outcomes and to determine what monitoring strategies they need to undergo. The recommendations are based on the evidence found and on the committee's knowledge and experience. A full discussion can be found in the committee's discussion of the evidence in evidence report I.
Hyperparathyroid UK Action 4 Change	Guideline	21	29	The guidelines state that no substantial resource impact, many patients give up waiting for NHS surgery due to the difficulty and timeframe in being diagnosed and often lengthy number of tests, scans. They seek private treatment, in which re-operations are available, so why not the case within the NHS? It should not be a case of only if you can afford it you can have the chance to be cured.	Thank you for your comment. When mentioning resource impact in the guideline we are referring to the potential impact of implementing the recommendations on the NHS compared to what already occurs in current practice.

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Hyperparathyroid UK Action 4 Change	Guideline	22	25	Totally agree surgery is the only current cure for a progressive disease.	Thank you for your comment.
Hyperparathyroid UK Action 4 Change	Guideline	22 23	27 - 29 1 - 2	2.85 does not accurately reflect the level at which their symptoms are worst. It is well known by many surgeons, and also within our organisation, that the level of calcium does not dictate the severity of symptoms. We have seen members experience relief from symptoms using cinacalcet with much lower levels of calcium, although it is very important to monitor to avoid hypocalcemia and it should be recommended as an interim measure before surgery. Both these points needs mentioning in association with cinacalcet.	Thank you for your comment. Cinacalcet acts to decrease serum calcium and therefore the committee considered the largest benefit would be in people with an adjusted serum calcium level above the reference range and symptoms resulting from their hypercalcaemia. The committee discussed the cut-off values for hypercalcaemia and use of cinacalcet. The clinical benefit in quality of life in the evidence in evidence report I was judged to be in people with an adjusted serum calcium level above 2.85 mmol/litre. Therefore, the cut-off was set at 2.85 mmol/litre for people with symptoms of hypercalcaemia. For the cut-off to define hypercalcaemia in the presence or absence of symptoms, the committee agreed from clinical experience that this should be set at above 3.0 mmol/litre, largely due to the increased risk of hypercalcaemic crises that may be seen with this degree of hypercalcaemia. The committee in accordance with the BNF view felt that continued biochemical monitoring should occur irrespective of symptoms. The committee from their experience stated that if there is any improvement and return to the adjusted serum calcium reference range with cinacalcet, treatment should be continued at the minimum effective dose to maintain that state, as discontinuation of the cinacalcet will lead to raised calcium and the symptoms are likely to return. If cinacalcet is deemed effective, it would become potentially chronic therapy.
Hyperparathyroid UK	Guideline	23	1 - 13	We are very concerned that people with	Thank you for your comment. Cinacalcet acts to

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Action 4 Change				calcium above the population reference range of 2.6mmol/l and below 2.85mmol/l have been completed excluded here and throughout the entire guideline which actually accounts for the majority of people with primary hyperparathyroidism and also the majority of people who are suffering very poor quality of life on a 'watch and wait' system, despite recorded hypercalcemia. Your guideline for hypercalcemia https://cks.nice.org.uk/hypercalcaemia states: '*covers the management of people with hypercalcaemia for whom the cause has not been confirmed. This includes the management of people with suspected cancer, but does not include people with suspected hyperparathyroidism'* So please could you inform us why they are not accounted for and the reasons they are excluded from your aims to '*to improve recognition and treatment of this condition, reducing long-term complications and improving quality of life' as stated on page 1 line 7?.*	decrease serum calcium and therefore the committee considered the largest benefit would be in people with an adjusted serum calcium level above the reference range. Therefore, most benefit will be achieved in people with a high serum calcium level and symptoms resulting from their hypercalcaemia. Our thresholds of albumin-adjusted serum calcium level above 2.85 mmol/litre with symptoms and an albumin-adjusted serum calcium level of 3.0 mmol/litre with or without symptoms align to our recommendations for surgery, i.e. patients with an albumin-adjusted serum calcium level above 2.85 mmol/litre are more likely to be symptomatic and at risk of events such as hypercalcaemic crisis (recommendation 1.3.1). Patients with an albumin-adjusted serum calcium level 2.6–2.85 mmol/litre are eligible for surgery (recommendation 1.3.2). The committee noted that cinacalcet should be an option in people who are unable to undergo surgery only and not as an alternative to surgery, as parathyroidectomy is the only definitive treatment option in people with primary hyperparathyroidism without surgical contraindication. Cinacalcet does not directly stop bone loss or kidney problems due to primary hyperparathyroidism. The committee wanted to make it clear that the common symptoms of hypercalcaemia should lead to diagnostic testing. The committee discussed that people with symptoms of hypercalcaemia such as thirst, polyuria and/or constipation should have albumin-adjusted serum calcium testing, as primary hyperparathyroidism is a common cause of raised calcium levels. The committee noted that there were

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					other non-PTH related causes of hypercalcaemia such as malignancy, granulomatous conditions such as sarcoidosis and tuberculosis, drugs such as thiazide diuretics, etc but they were not prioritised during the scoping process of this guideline.
Hyperparathyroid UK Action 4 Change	Guideline	24	15 - 20	The committee agreed that long-term monitoring for these people (increased risk of renal stones and fractures in people who have not had parathyroid surgery) is essential so that surgery can be offered when needed. Some of our members wished to reinforce that whilst they may not have suffered renal stones or fractures, the impact of long term monitoring had a detrimental impact on their lives which was only corrected by surgery. Not everybody with primary hyperparathyroidism will get kidney stones or suffer fractures. Their comments to follow:	Thank you for your comment. The committee from clinical experience noted that primary hyperparathyroidism patients have lower bone density, increased fracture risk and osteoporosis risk, and surgery reduces the risk of fracture in such patients. The committee also discussed that kidney stones are one of the end organ effects of primary hyperparathyroidism and the risk of developing renal stones decreases after surgery. Hence the committee agreed that surgery should be considered in people who have risk factors which are predictors of end organ disease or progressive disease to avoid further deterioration in health. We have edited the table for monitoring to direct people to the recommendations (actions) that should be taken following a positive monitoring test. Evidence report C on indications for surgery and evidence report E on surgical interventions included health related quality of life as an outcome.
Hyperparathyroid UK Action 4 Change	Guideline	24	25	'*The committee note people with multigland disease have a higher risk of reoccurrence'*. If only 1 gland is looked at and removed during surgery, how can you tell if the patient has multigland disease? It is obvious, and common sense; to carry out a 4 gland assessment is the best possible way of knowing how many glands are affected. Again, if procedures are carried out correctly it eliminates the chance of a second or third	Thank you for your comment. We recommend that a choice of focused parathyroidectomy or 4-gland exploration is offered to people with an identified single adenoma. The benefits and risks of each approach should be explained to the person so that they can make an informed choice. The role of titanium clips was not identified as a topic for inclusion during the scoping stakeholder consultation.

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				surgery being necessary and therefore cost is kept to a minimum and less chance of the patient suffering from reoccurrence needlessly. It also makes complete sense to attach a titanium clip to the glands that are left in situ for future location id needed.	
Hyperparathyroid UK Action 4 Change	Guideline	25	2 - 3	This shows a considerable lack of understanding on behalf of the committee. How is one supposed to determine pre surgery whether a person has multigland disease as it has been established repeatedly that scans are not consistently reliable, and that a large number of people who show one enlarged gland on a scan are found to have more than one enlarged gland upon surgical investigation. This suggestion really is not at all practical or feasible.	Thank you for your comment. The page number does not match the comment but we assume that you are referring to types of surgery based on solitary adenoma or multigland disease. We do not preclude the practice of 4-gland exploration in people who have had preoperative imaging that shows a single adenoma in the neck. We have now added what information should be provided to recommendation 1.4.6.
Hyperparathyroid UK Action 4 Change	Guideline	25	2 - 3	I think that the syndromes should actually be mentioned here to assist GP's who are unaware of them	Thank you for your comment. The comment does not match the page number but we assume you are referring to page 28 line 29. The committee agreed that those with multigland disease will benefit from a specialist with knowledge of associated syndromes. We anticipate that by reading this guideline health professionals will access high quality materials to supplement their knowledge of these syndromes.
Hyperparathyroid UK Action 4 Change	Guideline	25	8 - 10	Consistent reference to 'little or evidence' when there have been so many surgeries carried out over the years! The BAETS surgeons lists show just how many each year they perform, although we know not all our parathyroid surgeons contribute to this list, so why on earth is there little or no evidence? Using the records of every or even some of the patients that have blood tests for suspected	Thank you for your comment. The statements reflect the evidence that was identified that met the evidence review protocol for the review question.

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				PHPT, (continuing on to diagnosis and then surgery or being in the watch and wait category) would be enough evidence to prove how common normocalcemic and normohormonal PHPT cases are. Using the above, they could clearly show how important it is for all primary care workers to be acutely aware of the signs of PHPT even before bloods are taken.	
Hyperparathyroid UK Action 4 Change	Guideline	25	8 - 10	Our organisation were contacted over 18 months ago to assist with completion of the archaic Quality of Life surveys both pre and post op. It was acknowledged as archaic and consequently mostly irrelevant by us as well as the consultant who requested our assistance. We were promised a more up to date questionnaire that could have given you the information mentioned here, but it did not materialise. A wasted opportunity in my opinion.	Thank you for your comment. The survey was not related to this guideline.
Hyperparathyroid UK Action 4 Change	Guideline	27	8	Totally agree, constantly correcting the use of thyroid rather than parathyroid in discussions.	Thank you for your comment.
Hyperparathyroid UK Action 4 Change	Guideline	27	9	Totally agree but there does seem to be a lack of knowledge about normocalcemic hyperparathyroidism and the appropriate suppressive see-saw relationship between calcium and PTH within the NHS.	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people

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					with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Guideline	27	23 - 24	I think hyperplasia and parathyroid cancer should be mentioned here as other causes, not only because they are in most international research papers; an adenoma is not the only reason why parathyroid glands secrete excess parathyroid hormone, and also because we have members in our group who have/had both hyperplasia and parathyroid cancer although the latter is rare.	Thank you for your comment. The purpose of this section is to provide a context for the guideline and mentions the areas that are covered by the recommendations.
Hyperparathyroid UK Action 4 Change	Guideline	27	26	*'one of the most'* needs to be replaced with *'Primary Hyperparathyroidism is known and well documented to be the third most common endocrine disorder after diabetes and hypothyroidism in the UK, and the most common endocrine disorder in the US, who are far more advanced in research and statistics than the UK.*	Thank you for your comment. The purpose of this section is to provide a context for the guideline and mentions the areas that are covered by the recommendations. We are unable to comment on the quality of the statistics from different countries.
Hyperparathyroid UK Action 4 Change	Guideline	27	26 - 27	Perhaps this should read 'About 1 to 4 people per 1000 are known **to** have the condition.' as it is likely underdiagnosed until appropriate guidelines for medical professionals are in place.	Thank you for your comment. We have edited the sentence as suggested.
Hyperparathyroid UK Action 4 Change	Guideline	28	1 - 2	Primary hyperparathyroidism may be most commonly diagnosed between the ages of 50-60, but in our experience, by the time they are diagnosed, many have had the condition and symptoms for decades before diagnosis. Whilst your current guideline advocates surgery for people under 50, as does the Hammersmith Endocrine Bible, it appears surgeons are thankfully disregarding this	Thank you for your comment. We do not recommend any age cut-offs for surgery.

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				current recommendation. The British Association of Endocrine and Thyroid Surgeons Fifth National Audit Report 2017 quotes the following numbers of surgeries for primary hyperparathyroidism at surgery by age: There were 31 unspecified ages. < 21: 95, 21-30: 274. 31-40: 607, 41-50: 1,509, 51-60: 2,601, 61-70: 3,332, 71-80: 2,405, >80: 609	
Hyperparathyroid UK Action 4 Change	Guideline	28	3 - 4	*'The signs and symptoms of primary hyperparathyroidism are predominantly brought about by hypercalcaemia'* should be followed by *'although 25% of the hyperparathyroid population have Normocalcemic levels and a further 22.5% of the hyperparathyroid population have Normohormonal levels. Therefore it is necessary to look for an inappropriate negative feedback. Negative feedback is a reaction that causes a decrease in function, It occurs in response to stimulus causing the output of a system to be lessened; so the feedback tends to stabilise the system, referred to homeostasis'*	Thank you for your comment. The guideline does address normocalcaemic PHPT and recognises that PTH can be within the reference range. The algorithms and cut-off levels of calcium and PTH do take this into account. The aim of this section is to provide a brief context for the recommendations.
Hyperparathyroid UK Action 4 Change	Evidence Review A	3	1	Disclaimer *'The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement,*	Thank you for your comment. The disclaimer is standard text included in all NICE guidelines. Consensus methods have been used to develop the recommendations where limited evidence has been identified. We believe that this guideline will raise

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				professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users' Careful consideration of 'no evidence available' or 'little evidence available', which appears continuously through this guideline. We find this statement wholly unacceptable considering many of the recommendation made by your committee pose a danger to the life and wellbeing of people with primary hyperparathyroidism, and the only saving grace is that these recommendations are not mandatory. If this guideline is not reviewed taking into account the dangers we have highlighted, then maybe you ought to expand this disclaimer to warn of the dangers to life of untreated primary hyperparathyroidism as detailed in the 4th international endocrine workshop.	awareness of PHPT and improve outcomes in people affected by PHPT.
Hyperparathyroid UK Action 4 Change	Evidence Review A	6	5	1.3 PICO Table. The following symptoms listed should also be listed in the guideline assuming doctors will not have time at an appointment to go through the evidence reviews. The only symptom from this evidence review listed in the guideline is constipation. It makes no logical sense to omit the other symptoms; fatigue, depression, muscle weakness ,constipation, stomach pain, loss of concentration, mild confusion, an incidental abnormal blood test result, neurocognitive	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion of the evidence in evidence report A. The guideline explains that testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience. Some symptoms are most robustly associated with hypercalcaemia of

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					primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hyperparathyroid UK Action 4 Change	Evidence Review A	6	5 - 6	We recommend this sentence be amended from: 'Primary hyperparathyroidism (PHPT) is usually diagnosed as a result of investigation of hypercalcaemia' to: Primary hyperparathyroidism (PHPT) is usually diagnosed as a result of investigation for hypercalcaemia based on symptoms or an incidental finding of hypercalcemia.	Thank you for your comment. We have edited the sentence in accordance with your suggestion.
Hyperparathyroid UK Action 4 Change	Evidence Review A	6	5 - 6	In our experience an incidental finding of hypercalcemia is rare compared to hypercalcemia being missed year upon year; up to decades, when patients are faced with symptoms unrecognised by their doctors. In order to raise awareness and alert our doctors to look for hypercalcemia first before referring us to a rheumatologist for suspected fibromyalgia or arthritis, it is really essential to keep that promise of trying to raise awareness by sticking to the evidence based facts. Because your committee members failed to	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have amended recommendation 1.1.2 to be inclusive of all non-differentiated symptoms associated with PHPT. We now list the common symptoms in the section 'terms used in this guideline' and in the committee's discussion of the evidence in evidence report A to reflect those mentioned in your comment on the most common symptoms. We expect that through the implementation of this

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				look for evidence, does not mean it isn't there. We, the patients requested these guidelines because we need an increased awareness and are beyond fed up with reading information that simply isn't true about this disease. Many of our members have done years of research.	guideline awareness of primary hyperparathyroidism will increase and outcomes for patients will be improved. We recognise the limited evidence base on which this guideline is based which was searched in accordance with the NICE guidelines manual (2014).
Hyperparathyroid UK Action 4 Change	Evidence Review A	6	5 - 6	I recommend these sentences be amended to read: Hypercalcaemia is often either picked up as an incidental finding on a blood test, or a blood test taken because of a clinical suspicion of hypercalcaemia, which is associated with specific symptoms such as thirst and frequent urination, fatigue, anxiety, headaches, bone and joint pain, general malaise and in many cases sleep disturbances, cognitive dysfunction and vision disturbances.	Thank you for your comment. The developers do not wish to change this wording as they consider the current wording to be clear.
Hyperparathyroid UK Action 4 Change	Evidence Review A	6	8 - 9	The reality of a patient calling their doctor to make an appointment because they are really thirsty and peeing excessively is absurd to us. These days even calling a doctor means waiting in a telephone queue all morning, getting past the receptionist and maybe a triage nurse if they are lucky, and offered an appointment in 4 weeks, by which time they may have been asked to bring in a urine sample which is tested with a dipstick for high blood sugar and told 'everything is normal' and sent on their way. These two symptoms alone do not indicate primary hyperparathyroidism at all. Patients will call their doctor with bone pain, mobility and join pain, insomnia, memory issues, feeling generally unwell for an extended period of time. The symptoms listed in Table 1.3 **must** be listed here and in the	Thank you for your comment. Limited evidence, and the committee's clinical experience, suggests that primary hyperparathyroidism is more common in people who have symptoms of hypercalcaemia or have had a fragility fracture or a renal stone. In addition, the committee noted that primary hyperparathyroidism is most often discovered after a routine blood test that shows a raised serum calcium level but there is a group of patients where primary hyperparathyroidism is discovered due to skeletal or renal complications. The committee discussed that a moderately high prevalence of primary hyperparathyroidism in patients with renal stones and fractures (fragility fractures) suggests that primary hyperparathyroidism enhances the risk of these clinical events. Hence they agreed that people with such conditions would also require albumin-adjusted serum calcium testing to explore

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				main guideline.	possible hypercalcaemia and primary hyperparathyroidism. The committee agreed that although kidney stone formation due to primary hyperparathyroidism is not common, it is important to test for hypercalcaemia as quicker diagnosis and management of primary hyperparathyroidism would lead to a reduction in kidney stone risk over time. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience.
Hyperparathyroid UK Action 4 Change	Evidence Review A	6	9 - 10	I recommend this sentence be amended to: While some people with PHPT may believe themselves to be asymptomatic, it is possible they have dismissed different symptoms including depression, tiredness, worsening memory, aching joints, vision and sleep disturbances, constipation, and headaches as age or lifestyle related.	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have amended recommendation 1.1.2 to be inclusive of all non-differentiated symptoms associated with PHPT. We now list the common symptoms in the section 'terms used in this guideline' and in the committee's discussion of the evidence in evidence report A to reflect those mentioned in your comment on the most common symptoms.
Hyperparathyroid UK Action 4 Change	Evidence Review A	6	10 - 12	I recommend this sentence be amended to: Some people with PHPT develop renal stones, gall stones, salivary stones, and some may	Thank you for your comment. The aim of this section of the review in particular is to serve as a brief chapter introduction and hence more detailed information on

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				experience fractures due to low bone mineral density or osteoporosis.	what may be relevant to part of the population with PHPT is beyond its remit.
Hyperparathyroid UK Action 4 Change	Evidence Review A	7	1 - 8	1.4 Clinical Evidence. You conducted a search for studies in people presenting with symptoms of primary hyperparathyroidism to identify the indications for testing for PHPT, including symptoms and any incidental blood test result yet no clinical evidence was identified for this question. I feel you have wasted an opportunity to obtain this information from 1398 people with primary hyperparathyroidism within our organisation. I fully expect we can still provide you with this information within 7-14 days of request to include clinical notation. We offered our services at the beginning of consultation on this guideline in 2016.	Thank you for your comment. The guideline was developed in accordance with the NICE guidelines manual (2014). NICE guideline development methods processes have been followed throughout the development of this guideline. Evidence from randomised controlled trials (RCT) has been prioritised, as these are viewed as of the highest quality for questions on interventions and diagnosis due to their rigorous design that makes them the least susceptible to bias. This has been done to ensure the resulting recommendations are based on the best available evidence. Where no RCT evidence has been available or when RCTs are not the most appropriate study design to answer the question, the committee has considered looking at non-randomised evidence/lower quality evidence a priori on a question-by-question basis. In areas where no such clinical evidence was identified, the committee used their collective experience to make consensus recommendations. The committee also identified areas where evidence to answer their review questions was lacking and have used this information to formulate recommendations for future research. The committee was comprised of people with knowledge and experience of primary hyperparathyroidism. How the committee made the recommendations is captured in the committee's discussion of the evidence in the evidence reports and in the rationale and impact sections of the short guideline. . We expect that the guideline will increase awareness

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					of primary hyperparathyroidism including the wide range of symptoms that people may experience. We have sought to make clear recommendations on when advice from a specialist should be sought. All people with the condition should now be considered for referral for surgery. The guideline should reduce variation in practice and improve outcomes for people affected by the condition.
Hyperparathyroid UK Action 4 Change	Evidence Review A	12	19	*Do not measure ionised calcium when testing for primary hyperparathyroidism.* Ionised calcium is more accurate and considered as the gold standard. It removes the variability caused by albumin adjustments. It should be used once an initial diagnosis is suspected	Thank you for your comment. In the experience of the committee it is not necessary to measure ionised calcium. They discussed that ionised calcium testing cannot be done in primary care and it would usually be undertaken using a blood gas analyser in hospital. They considered that as ionised calcium measurement is a point-of-care test it is not subject to stringent quality control like laboratory- based tests. Furthermore the sample has to be handled very quickly, making it a less reliable test.
Hyperparathyroid UK Action 4 Change	Evidence Review A	13	6	*Do not routinely repeat PTH measurement in primary care.* If pth is not measured more than once how will the relationship between the calcium and pth be assessed? The relationship between PTH and calcium is of paramount importance when diagnosing phpt as it is the lack of a suppressive relationship between the two that provides the diagnosis. It is crucial to obtain more than one concurrent pth and calcium.	Thank you for your comment. We do recommend that PTH testing should be done with contemporaneous albumin-adjusted serum calcium testing, as it is necessary to interpret the PTH result in the context of the albumin-adjusted serum calcium level.
Hyperparathyroid UK Action 4 Change	Evidence Review A	13	21	This seems to imply that there are known specialist centres for re-operative parathyroid surgery. If these guidelines are to assist primary care givers then needs to be more specific, who are these experts, where are these centres, how can they be easily	Thank you for your comment. NICE guidelines are unable to recommend specific centres.

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				accessible to patients in all areas of the country.	
Hyperparathyroid UK Action 4 Change	Evidence Review A	15	8 - 9	The list of symptoms needs to be widened. Not everyone suffers from those listed and it should include bone pain, muscle weakness, cognitive dysfunction and more. Bone pain doesn't appear as a listed symptom - and may well affect people who don't have either osteoporosis or a fracture. The evidence that phpt causes calcium to be drawn from your bones is clear - why not include it as a symptom?	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have removed the examples from recommendation 1.1.2 and now list the common symptoms based on those provided by you in the section 'terms used in this guideline'. We have amended the list of symptoms in the rationale and committee's discussion of the evidence in evidence report A. We explain how testing for albumin-adjusted serum calcium should be done on a case-by-case basis because of the wide range of symptoms people can experience.
Hyperparathyroid UK Action 4 Change	Evidence Review A	17	17 - 22	The NICE Clinical Knowledge Summary for hypercalcaemia (https://cks.nice.org.uk/hypercalcaemia#!topicsummary) lists a considerable number of clinical features of hypercalcaemia which are not listed within the guidelines. The guidelines should note that the suggested symptoms are not exhaustive and refer clinicians to the CKS by a hyperlink so that the full extent of clinical features of hypercalcaemia can be considered in deciding whether to measure albumin-adjusted serum calcium.	Thank you for your comment. The electronic NICE pathway on the NICE website will link to the Clinical Knowledge Summary.
Hyperparathyroid UK Action 4 Change	Evidence Review A	17	17 - 27	NICE should undertake a review into the numbers of patients who have the 'non-specific symptoms' to find out how many of them do recover to establish that there is a causal link between them and phpt. I had neither renal stones nor a risk of fracture or osteoporosis but did have most of the other symptoms, the	Thank you for your comment. The committee is unable to commission primary research.

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				majority of which have disappeared after the operation.	
Hyperparathyroid UK Action 4 Change	Evidence Review A	41	General	No evidence is mentioned in Evidence Review A 3 times. Please ask us to help with this.	Thank you for your comment. The guideline was developed in accordance with the NICE guidelines manual (2014). NICE guidelines prioritise evidence from randomised controlled trials, as these are viewed as of the highest quality for questions on interventions and diagnosis due to their rigorous design that makes them the least susceptible to bias. Where no RCT evidence was available or when RCTs are not the most appropriate study design to answer the question, the committee considered looking at non- randomised evidence/low quality evidence a priori on a question-by- question basis. The details of this can be found in the review protocols in appendix A. The same principles applied throughout whereby the committee considered that lower quality evidence was more likely to be unreliable and therefore may not assist in making recommendations. The committee considered that performing a systematic review of all lower quality studies would have taken a huge amount of resources and would not have assisted decision making. In areas where no clinical evidence was identified, the committee used their collective experience to make consensus recommendations. The committee noted that in some areas not making a recommendation would leave a gap and in such cases, expert guidance was better than none at all. The committee was comprised of people with knowledge and experience of the primary hyperparathyroidism. How the committee made the recommendations is captured in the committee's discussion of the evidence in the evidence reports and in the rational and impact sections of the

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					short guideline. However, the committee also identified areas where evidence to answer their review questions was lacking and have used this information to formulate recommendations for future research.
Hyperparathyroid UK Action 4 Change	Evidence Review A	41	1 - 2	Appendix D clinical evidence bone density table was conducted in Sweden in 2006: 167 women turned up for DX examination. 38 of these women had normal bone mineral density and 10 had a T-score below -3 and were excluded. 119 women age 58.9 years with 9.5 (1-19) years since last menstruation met the inclusion criteria and were called for further investigation. Of these women 20 were osteoporotic (T-score <-2.5) and 99 had osteopenia (T-score from -1 to 2.4). Their bone density values, measured (g/cm): L2.L4, 1.001 (0.813-1.354); femoral neck, 0.835 (0.680-1.129). All had wrist fracture within 5 years of entering the study. 12 of these women were smokers Only 8 of them were found to have PHPT. This study is irrelevant and superseded by far more modern studies. 12 years later we know that PHPT occurs in many women pre menopause. The lack of British studies does not mean studies have not been conducted. Occurrence rates in the US are statistically rated at 1 in 50 women and 1 in 80 men over 18.	Thank you for your comment. The guidance was produced in accordance with the NICE guidelines manual (2014). We do not include evidence that does not meet the criteria pre-specified in our evidence review protocols, to eliminate bias in the selection of the included evidence. The committee judged the older events to be applicable. Systematic searches for evidence are re-run prior to consultation, to identify and potentially include (depending on the extent to which they meet our protocols) any newly available research evidence that had not been considered at the time each evidence report had been conducted. The quality of the evidence included in our evidence reports is thoroughly assessed to dictate the extent to which the evidence identified can guide decision making which is then a result of not only the consideration of the included evidence but also clinical expertise.
Hyperparathyroid UK	Evidence	41	1 - 2	We conducted a study in our group in April	Thank you for your comment. We looked for evidence

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Action 4 Change	Review A			2018 regarding bone fractures. Here follow some responses which I feel indicates the importance of testing for primary hyperparathyroidism and a necessary emphasis in these guidelines of fractures as a symptom of PHPT	on bone fractures in evidence report I for monitoring and we did not find any evidence on this. However the committee has made recommendations on assessing and monitoring fracture risk in patients with primary hyperparathyroidism (recommendation 1.6).
Hyperparathyroid UK Action 4 Change	Evidence Review A	43	1	1 Table Di Monaco Study 2004. Based on a study of elderly patients admitted to a rehabilitation hospital after hip fracture either spontaneous or a result of minimal trauma. (404 postmenopausal women, and 40 men) aged 65 years and older. Not only is this study dated 14 years ago, but I fail to see its relevance as many of our members were between 10 and 30 years younger than this study when their fractures occurred and were consistently feet, wrists and ribs. Research is needed based on both male and female people with PHPT aged 30-60+	Thank you for your comment. The study by Di Monaco 2004 as well as the majority of individual studies included in evidence reviews has not been considered as representative of the wider population of patients with PHPT. The inclusion of this study in Evidence review A reflects the fact that as per NICE established processes for conducting evidence reviews, it has met the inclusion criteria specified in the protocol for that review which have not included a date cut-off, and informs the review question. As for every other review question, the recommendations made are not the result of the consideration of a single study such the aforementioned, but are rather a result of the consideration of the body of the evidence identified and the committee's clinical expertise. The extent to which decision making relies on the evidence included in reviews also depends on the quality of the evidence, and the quality of the evidence from this study has been deemed low. Areas for further research were identified by the guideline committee throughout development following the appraisal of the evidence. However, the committee did not prioritise PHPT aged 30–60+ for its research recommendations.
Hyperparathyroid UK Action 4 Change	Evidence Review A	44	1	1 Table Fuss Renal Stone Study dated 1987. Is the information on this table from 31 years ago relevant to a new 2018 guideline? I would	Thank you for your comment. Please note that we have cross-referred to the NICE guideline on renal and ureteric stones in the recommendations for monitoring. The study you refer to, although conducted many

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				recommend you read the NICE guideline on Renal and Uretic stones due for publication 8 January 2018 and reference it here as a more up to date source of information.	years ago as you have noted, met the criteria specified in our protocol and was therefore included in this review to be considered by the committee along with other pieces of evidence meeting our inclusion criteria. A date cut-off for studies was not part of the protocol inclusion/exclusion criteria (Appendix A) and hence all studies meeting the inclusion criteria irrespective of year of publication were included. However, the committee did take into account the year of publication when making recommendations. According to NICE processes for guideline development, it is very unlikely for recommendations to purely be based on a single study such as this and recommendations are a result of the committee's consideration of the evidence identified along with its strengths and limitations and their clinical expertise. The extent to which decision making relies on the evidence included in reviews also depends on the quality of the evidence, and the quality of the evidence from this study has been deemed low.
Hyperparathyroid UK Action 4 Change	Evidence Review A	44	1	1 Table This article written in 2012 from the Indian Journal of Endocrinology and Metabolism, is by far, a more modern study on renal stones and Primary hyperparathyroidism: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3313745/ Here is an abstract: Primary hyperparathyroidism (PHPT) is associated with nephrolithiasis and nephrocalcinosis. Hypercalciuria is one of the multiple factors that is implicated in the complex pathophysiology of stone formation. The presence of a renal stone (symptomatic or	Thank you for your comment. The guideline was developed in accordance with the NICE guidelines manual (2014). NICE guidelines prioritise evidence from randomised controlled trials, as these are viewed as of the highest quality for questions on interventions due to their rigorous design that makes them the least susceptible to bias. Where no RCT evidence has been available or when RCTs are not the appropriate study design to answer the question, the committee considered looking at non- randomised evidence/lower quality evidence and more specifically prospective/retrospective/cohort studies a priori on a question-by-question basis. The reference you provide is not a study, but an article that hence does not meet our pre-specified inclusion

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				asymptomatic) categorizes PHPT as symptomatic and is an indication for parathyroid adenomectomy. Progression of nephrocalcinosis is largely reversible after successful surgery, but the residual risk persists. PHPT is also associated with declining renal function. In case of asymptomatic mild PHPT, annual renal functional assessment is advised. Guidelines suggest that an estimated glomerular filtration rate (eGFR) < 60 ml / minute / 1.73 m2 is an indication for parathyroid adenomectomy. This article discusses how to monitor and manage renal stones and other related renal parameters in case of PHPT.	criteria that can be found in Appendix A of Evidence review A.
Hyperparathyroid UK Action 4 Change	Evidence Review A	48	1	Sharma Study Sharma Study 2017 Results. *Protocol outcome 1: Diagnosis of PHPT -Actual outcome: Diagnosis of PHPT: 19/381 (5%); Males: 8, Females: 11; this was reported to be 10 to 20 times higher than the prevalence of PHPT in the general population.* Where is the evidence for 'this was reported to be 10 to 20 times higher than the prevalence of PHPT in the general population?' Given that 'extra comments' on previous page 47 reports; *Diagnosis of PHPT was based on the following criteria: serum Ca ≥10.2 mg/dL with clearly elevated (>70 pg/mL) or non-suppressed iPTH (>25 pg/mL) or elevated iPTH but normal serum Ca after exclusion of secondary PHPT and histologically confirmed parathyroid adenoma or hyperplasia,* I believe if the above criteria for diagnosis of primary	Thank you for your comment. Sharma 2017 reported that the diagnosis of PHPT in that study was 10 to 20 times higher than the prevalence of PHPT in the general population in India at the time; we have extracted this information as it was reported in the paper. The recommendations formulated aim to encompass and be relevant to the diagnosis of the majority of patients with PHPT rather than being specifically relevant to a distinct type of PHPT in particular. Following the consideration of the whole body of evidence included in review A and their clinical expertise, the committee considered that the measures specified in the recommendations best capture the way PHPT can be appropriately diagnosed in the majority of patients. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT

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				hyperparathyroidism within the general population were actually applied to all with suspected PHPT whether symptomatic or asymptomatic, then an increased number of people will be positively diagnosed. Currently many doctors and endocrinologists are failing to recognise an elevated iPTH but normal serum Ca after exclusion of secondary Hyperparathyroidism (HPT) is in fact a distinct type pf primary Hyperparathyroidism. It would be helpful if this criteria is referenced in the actual guideline on page 3.	presentations, but on balance will identify most people. People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). No substantive objective was identified data on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Evidence Review A	49	2	Walker Study Though this study is dated 2013, the data encompassed in the database created in 1996 covers patients with stones from 1990 to 2007 with an average age of 49. I don't see any relevance or use to this guideline, as an acceptable treatment for primary hyperparathyroidism in 1996 for post-menopausal women was estrogen rather than surgery. As there is no follow up or final outcome for these patients I believe it is of no use in this guideline unless you intend to highlight aspects such as: *Diagnosis of PHPT was based on demonstration of sustained hypercalcaemia and verified at surgery,* which differs from the previous study (Sharma Study) in less effective diagnosis criteria, likely resulting in significantly less people being successfully diagnosed. One has to ask 'where are those poor people now and did they ever get a diagnosis?' One will likely never know! This study would likely be better added to page	Thank you for your comment. Both studies you mention met the inclusion criteria pre-specified in the review protocol and were therefore included in the review. The concerns you raise have been taken into account both by the developer and the guideline committee and are reflected in the quality assessment of the evidence which then determines the extent to which decision making has been based on the evidence identified.

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				56 excluded studies list.	
Hyperparathyroid UK Action 4 Change	Evidence Review B	General	General	No evidence is mentioned in Evidence Review B 4 times. Please ask us to help with this	Thank you for your comment. The guideline was developed in accordance with the NICE guidelines manual (2014). NICE guidelines prioritise evidence from randomised controlled trials as these are viewed as of the highest quality for questions on interventions and diagnosis due to their rigorous design that makes them the least susceptible to bias. Where no RCT evidence was available or when RCTs are not the appropriate study design to answer the question, the committee considered looking at non randomised evidence/low quality evidence a priori on a question-by- question basis. The details of this can be found in the protocols in appendix A. The same principles applied throughout whereby the committee considered that lower quality evidence was more likely to be unreliable and therefore may not assist in making recommendations. The committee considered that performing a systematic review of all lower quality studies would have taken a huge amount of resources and would not have added a great deal to the guideline. In areas where no clinical evidence was identified, the committee used their collective experience to make consensus recommendations. The committee noted that in some areas not making a recommendation would leave a gap and in such cases, expert guidance was better than none at all. The committee was comprised of people with knowledge and experience of primary hyperparathyroidism. How the committee made the recommendations is captured in the committee's discussion of the evidence in the evidence reports and in the rational and impact sections of the short guideline.

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					However, the committee also identified areas where evidence to answer their review questions was lacking and have used this information to formulate recommendations for future research.
Hyperparathyroid UK Action 4 Change	Evidence Review B	5	15	Table 1 Given the committee's definition of Population 2 as those "Presenting with an adjusted serum calcium level within the reference range (2.2-2.6mmol/L) but would be suspected to have PHPT due to end-organ damage or an incidental raised PTH level. These people would have suspected normocalcaemic PHPT." I fail to see how those who fall into this population would have an incidental raised PTH level whilst their serum calcium level remains in the reference range as there would be no reason for them to have a PTH test.	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Evidence Review B	12	11 - 12	Again, this symptoms relate more to diabetes rather than PHPT and the list needs to reflect the symptoms listed in Evidence Review A Pico Table 1.3 and our comments in relative paragraphs of guideline.	Thank you for your comment. In the knowledge and experience of the committee these are the symptoms strongly associated with hypercalcaemia.
Hyperparathyroid UK Action 4 Change	Evidence Review B	12	21	How has the diagnostic guideline of 2.5 been derived? On what evidence has this been based? We have provided evidence in the guideline that the relationship between calcium and PTH is the necessary numbers to consider to correctly diagnose all classifications of PHPT	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an

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					albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4) . People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Evidence Review B	13	2	How has the diagnostic guideline of 2.5 been derived? On what evidence has this been based? We have provided evidence in the guideline that the relationship between calcium and PTH is the necessary numbers to consider to correctly diagnose all classifications of PHPT	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4. People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B.
Hyperparathyroid UK Action 4 Change	Evidence Review B	15	34 - 5	I welcome the recommendation of a contemporaneous calcium test alongside the PTH test	Thank you for your comment.
Hyperparathyroid UK Action 4 Change	Evidence Review B	17	2 - 4	*The committee noted that the vast majority of presentations of primary hyperparathyroidism are in people with hypercalcaemia*. If the diagnosis of primary hyperparathyroidism is based on a set lower limit of calcium then of course the majority of presentations will be	Thank you for your comment.

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				above that limit? If you always do what you've always done you will always get what you always got.	
Hyperparathyroid UK Action 4 Change	Evidence Review C	General	General	No evidence is mentioned here 13 times. Please ask us to help you with this.	Thank you for your comment. The guideline was developed in accordance with the NICE guidelines manual (2014). NICE guidelines prioritise evidence from randomised controlled trials, as these are viewed as the most rigorous design and are least susceptible to bias for answering intervention questions. Where no RCT evidence is available, the committee considered non-randomised evidence/low quality evidence a priori on a question-by-question basis. The details of this can be found in the protocols in appendix A. The same principles applied throughout whereby the committee considered that lower quality evidence was more likely to be unreliable and therefore may not assist in making recommendations. The committee considered that performing a systematic review of all lower quality studies would have taken a huge amount of resource and would not have assisted decision making. In areas where no clinical evidence was identified, the committee members used their collective experience to make consensus recommendations. The committee noted that in some areas not making a recommendation would leave a gap and in such cases, expert guidance was better than none at all. The committee was comprised of people with knowledge and experience of the primary hyperparathyroidism. How the committee made the recommendations is captured in the committee's discussion of the evidence in the evidence reports and in the rational and impact sections of the short guideline.

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					However, the committee also identified areas where evidence to answer their review questions was lacking and have used this information to formulate recommendations for future research.
Hyperparathyroid UK Action 4 Change	Evidence Review C	7 25	13 - 14 41 - 43	*"The committee wanted to move away from classifying people as symptomatic and asymptomatic."* *"The committee also considered the cost effectiveness of surgery for those who do not meet these criteria - an 'asymptomatic' population"* The committee have reverted to using terminology which they wanted to move away from despite acknowledging on p 7, line 12-13 that "*absence of symptoms may not necessarily indicate milder disease, as end-organ effects can be present without symptoms*"	Thank you for your comment. The term 'asymptomatic' is only used where there is reference to the NIH criteria for parathyroidectomy in asymptomatic patients. No distinction was made between symptomatic and asymptomatic patients in the analysis nor did the committee make separate recommendations for symptomatic and asymptomatic patients.
Hyperparathyroid UK Action 4 Change	Evidence Review C	23	45 - 49	The committee agreed not to make a recommendation for surgery for patients with non-specific symptoms. Is this the case even with an elevated calcium and an inappropriately suppressed pth?	Thank you for your comment. No evidence was identified to support a recommendation to offer surgery for people with non-differentiated symptoms. The guideline does recommend that surgery is considered in such people with a discussion of the benefits and risks for the individual. In accordance with the recommendations the GP would seek advice from a specialist with an interest/expertise in PHPT. Elevated calcium and PTH level below the midpoint of the reference range is compatible with the diagnosis of primary hyperparathyroidism. Confirmed diagnosis of PHPT and referral to surgery will be made for those with positive tests following recommendation 1.1.8 and excluding FHH following recommendation 1.2.2.
Hyperparathyroid UK Action 4 Change	Evidence Review C	23	49 - 51	*"the committee noted that PHPT is associated with a decline in renal function but there is no*	Thank you for your comment. The guideline contains recommendations on who should be referred for

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				evidence that parathyroidectomy leads to an improvement". On the following page, (Page 24, lines 28-30 of Evidence C), it is noted that *"the committee, from their clinical experience, also discussed that kidney stones are one of the end organ effects of PHPT and the risk of developing stones decreases after surgery".* Would that not suggest that a parathyroidectomy, therefore, is key to the **prevention** of a decline in renal function in patients who have not yet developed kidney disease, since the risk of developing stones decreases following surgery? Surely this is evidence that a patient with PHPT who does not have renal function decline should be eligible for surgery and therefore that the criteria for surgery as regards kidney function/stones is irrelevant? Is it really too much to expect patients not to have to develop life-changing disease in order to warrant surgical intervention? Does this depict a wise, healthful approach when considering eligibility for surgery? There is no need to mention end organ disease in the criteria for surgical referral, surgical referral is a must for all patients. Perhaps those whom have already developed end organ disease should be referred as 'urgent', which would seem a much less complicated way of listing the criteria as laid out in this draft.	surgery including a 'consider' recommendation for all people with a diagnosis of PHPT.
Hyperparathyroid UK Action 4 Change	Evidence Review C	24	39 - 41	I welcome the guidelines not wishing to make a distinction relating to age thus ensuring equality of access to surgery	Thank you for your comment.
Hyperparathyroid UK Action 4 Change	Evidence Review C	24	43 - 45	Whilst welcoming that the committee emphasise consideration regarding treatment	Thank you for your comment. This paper was identified in our search, but did not meet the criteria for inclusion

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				is more about life expectancy I am surprised that they have not referenced the cost-effectiveness analysis by Zanocco K, Sturgeon C. (*Surgery* 2008; 144:290–8.). This study is included on the NHS Economic Evaluation Database and concludes that, for asymptomatic patients with primary hyperparathyroidism over the age of 50 years, parathyroidectomy was the most cost-effective strategy when predicted life expectancy was above five years, while observation was the most cost-effective strategy when predicted life expectancy was below five years.	in the review as it is from a US perspective.
Hyperparathyroid UK Action 4 Change	Evidence Review C	24	7 - 9	*They felt that it was reasonable to define a threshold of 2.85mmol/L or above at which surgery would be recommended'.* This is nonsensical - a diagnosis is provided at a level of 2.5 and above but no surgery is available until the level goes above 2.85. Quite clearly the experts on the committee have no understanding of how phpt works - once your calcium is elevated, however, minimally, you feel ill and your quality of life is compromised. The degree of elevation of the calcium has no bearing on the severity of the symptoms. This arbitrary cut off discounts everyone with normocalcaemic primary hyperparathyroidism whose calcium never goes above the normal range and everyone with a high albumin causing a lower adjusted calcium. I never had an adjusted calcium level over 2.8 but I had a partial parathyroidectomy in May 2018 with the removal of 1 adenoma and my calcium and pth levels then returned to normal.	Thank you for your comment. This guideline is permissive about surgery in all people with a confirmed diagnosis of primary hyperparathyroidism (recommendation 1.3.2 and recommendation 1.3.1).
Hyperparathyroid UK	Evidence	24	7 - 9	Why did the committee feel it was reasonable	Thank you for your comment. All of the relevant

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Action 4 Change	Review C			to define a threshold of 2.85mmol/litre or above at which surgery would be recommended? On what evidence was this based? Given that previous guidelines utilise this figure what research was undertaken into the evidence base underpinning these consensus based recommendations, given that these recommendations are based on research current in 2013, ie over five years old?	literature was searched up to 6 August 2018. The committee acknowledges that some of the evidence was of low quality or outdated, and in these instances took this into account when making recommendations. Where evidence was low quality, the committee also considered factors such as current practice, and clinical experience. How the committee made the recommendations is captured in the committee's discussion of the evidence in the evidence reports and summarised further in the rational and impact sections of the guideline. As specified in the committee's discussion of the evidence, the committee noted that there was no evidence to support a particular cut-off point for adjusted serum calcium requiring surgery but they considered that it was reasonable to define a threshold of 2.85 mmol/litre or above at which surgery would be recommended. Recommendation 1.3.2 recommends that a referral for surgery is considered in all people diagnosed with primary hyperparathyroidism irrespective of the presence of the features listed in recommendation 1.3.1.
Hyperparathyroid UK Action 4 Change	Evidence Review C	25	32 - 33	It remains unclear why the guideline states a calcium level of 2.85 as a cut off point. Studies such as Bargren et al show that significant hypercalcemia was associated with nephrolithiasis, but interestingly, patients with milder hypercalcemia had significantly more depression, bone or joint pain, and constipation, suggesting that these symptoms are likely not mediated by hypercalcemia. (References on next line)	Thank you for your comment. This is a questionnaire study, the study design of which limits our confidence in the reliability of its findings and constrains our ability to make recommendations based on them, as it does not meet NICE's criteria of the best available evidence. NICE guidelines prioritise evidence from randomised controlled trials, as these are viewed as of the highest quality for questions on interventions due to their rigorous design that makes them the least susceptible to bias. Where no RCT evidence was available or when RCTs are not the appropriate study design to answer the question, the committee considered looking at non-randomised evidence/lower quality evidence a priori on a question-by-question basis. The details of

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					this can be found in Appendix A of each evidence review. The same principles applied throughout whereby the committee considered that lower quality evidence was more likely to be unreliable and therefore may not assist in making recommendations. The committee members also used their collective experience to make consensus recommendations and 2.85 mmol/litre as a cut-off for albumin-adjusted serum calcium levels has been based on the committee's clinical expertise.
Hyperparathyroid UK Action 4 Change	Evidence Review C	25	32 - 33	Bargren, A.E., Repplinger, D., Chen, H. and Sippel, R.S., 2011. Can biochemical abnormalities predict symptomatology in patients with primary hyperparathyroidism?. *Journal of the American College of Surgeons*, *213*(3), pp.410-414.	Thank you for your comment. This is questionnaire study, the study design of which limits our confidence in the reliability of its findings and constrains our ability to make recommendations based on them, as it does not meet NICE's criteria of the best available evidence. NICE guidelines prioritise evidence from randomised controlled trials, as these are viewed as of the highest quality for questions on interventions due to their rigorous design that makes them the least susceptible to bias. Where no RCT evidence was available or when RCTs are not the appropriate study design to answer the question, the committee considered looking at non-randomised evidence/lower quality evidence a priori on a question- by-question basis. The details of this can be found in Appendix A of each evidence review. The same principles applied throughout whereby the committee considered that lower quality evidence was more likely to be unreliable and therefore may not assist in making recommendations. The committee also used their collective experience to make consensus recommendations and 2.85 mmol/litre as a cut-off for albumin-adjusted serum calcium levels has been based on the committee's clinical expertise.
Hyperparathyroid UK	Evidence	7	1	Table	Thank you for your comment. Evidence from 56

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Action 4 Change	Review D			No evidence is mentioned in Evidence Review D 13 times. Please ask us to help you with this. It should be noted parathyroid venous sampling is not recommended on a patient who has had previous neck surgery due to the likelihood of false positive results.	studies that met protocol criteria were included in this review. NICE guidelines prioritise evidence from randomised controlled trials, as these are viewed as of the highest quality for questions on interventions and diagnosis due to their rigorous design that makes them the least susceptible to bias. Where no RCT evidence was available or when RCTs are not the most appropriate study design to answer the question, the committee considered non-randomised evidence/ lower quality evidence a priori on a question-by-question basis. Please see protocols in appendix A. We are confident that no further evidence meeting these criteria other than what is already included in the review is available to date.
Hyperparathyroid UK Action 4 Change	Evidence Review F	General	General	No evidence is mentioned in Evidence Review F 13 times. Please ask us to help you with this.	Thank you for your comment. We identified limited evidence that met the protocol criteria for people with failed surgery. NICE guidelines prioritise evidence from randomised controlled trials for questions on interventions, as these are viewed as the most rigorous design and are least susceptible to bias. Where no RCT evidence was available or when RCTs are not the most appropriate study design to answer the question, the committee considered non-randomised evidence/ lower quality evidence a priori on a question-by- question basis. Please see the review protocols in appendix A. The committee agreed from their collective experience that input from a multidisciplinary team at a specialist centre should be sought, noting that repeat parathyroid surgery is relatively uncommon; failure rates are higher than in primary surgery and it carries a higher risk (recommendation 1.4.12). As there was lack of sufficient evidence in this area they also made a recommendation for future research on management

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					after unsuccessful primary surgery.
Hyperparathyroid UK Action 4 Change	Evidence Review F	General	General	We are concerned with the lack of recent, relevant research undertaken on PHPT. We know there is an abundance of information available.	Thank you for your comment. The guideline was developed in accordance with the NICE guidelines manual (2014). NICE guidelines prioritise evidence from randomised controlled trials for questions on interventions, as these are viewed as the most rigorous design and are least susceptible to bias. Where no RCT evidence was available or when RCTs are not the most appropriate study design to answer the question, the committee considered looking at non- randomised evidence/low quality evidence a priori on a question-by- question basis. The details of this can be found in the protocols in appendix A. The same principles applied throughout the development process whereby the committee considered that lower quality evidence was more likely to be unreliable and therefore may not assist in making recommendations. The committee considered that performing a systematic review of all lower quality studies would have taken a huge amount of resource and would not have assisted decision making. In areas where no clinical evidence was identified, the committee used their collective experience to make consensus recommendations. The committee noted that in some areas not making a recommendation would leave a gap and in such cases, expert guidance was better than none at all. The committee was comprised of people with knowledge and experience of the primary hyperparathyroidism. How the committee made the recommendations is captured in the committee's discussion of the evidence in the evidence reports and in the rational and impact sections of the short guideline.

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					However, the committee also identified areas where evidence to answer their review questions was lacking and have used this information to formulate recommendations for future research.
Hyperparathyroid UK Action 4 Change	Evidence Review F	6	14	Table 1: PICO characteristics of review question. No mention of hyperplasia. In fact there is a definite lack of recommendation for hyperplasia in general.	Thank you for your comment. We have included hyperplasia as a population inclusion criteria in our protocol. However, we did not identify any evidence specifically in people with hyperplasia. Multigland disease is the preferred terminology for hyperplasia. We have included management of multigland disease in our recommendations.
Hyperparathyroid UK Action 4 Change	Evidence Review F	6	6	We are concerned that this figure of 4-5% not cured, could actually be higher due to the current lack of consistency in original diagnosis and also post op follow up and tests. Different trusts have different procedures. Some do not test pth during or after surgery. Some trusts are also not concerned in determining if PTH and calcium have established the correct suppressive relationship. If they inform patients, they are cured how many of these patients who know they feel unwell seek private surgery in order for a cure? Are these numbers included in the 4-5% of not cured?	Thank you for your comment. This information has been contributed from the guideline committee members who have drawn upon their knowledge and clinical expertise and are confident about its accuracy.
Hyperparathyroid UK Action 4 Change	Evidence Review F	6	6 - 8	*Surgery may fail to normalise serum calcium for a number of reasons including not removing the adenoma(s) or missing a diagnosis of FHH.* You have missed out: or removal of one or more hyperplastic glands. It is also entirely possible for remaining glands to become hyperplastic at a later date.	Thank you for your comment. The committee and the developer team acknowledge there are numerous reasons why surgery may fail to normalise serum calcium levels and have chosen to refer to two of the most frequently encountered in clinical practice. This information is only included as part of the introduction to one of the evidence chapters this guideline has been based on. Possible reasons for failed surgery have been addressed in more detail in the committee's discussion of the evidence.

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Hyperparathyroid UK Action 4 Change	Evidence Review F	6	8 - 10	We are concerned as to why there are differing views on offering repeat surgery. Patients of any age deserve equal treatment. More up to date research on current patient groups is needed to determine how this group can benefit from being cured, long term health implications of living with phpt can be costly to the NHS.	Thank you for your comment. In the knowledge and experience of the committee a multidisciplinary team review needs to be conducted at a specialist centre to discuss the benefits and risks for the individual. We have made a research recommendation on failed surgery: 'What is the best and most cost-effective management strategy for people whose first surgery for primary hyperparathyroidism is not successful?'
Hyperparathyroid UK Action 4 Change	Evidence Review F	18	18	*The committee noted that the indications for surgery are in line with current practice. Please note the comments on page 5 from members in our organisation dispute this.*	Thank you for your comment. In the knowledge and experience of the committee the indications for surgery are current practice with the exception that we recommend that people without the symptoms specified are still considered for referral. Additionally, age is not an indicator for surgery in this guideline.
Hyperparathyroid UK Action 4 Change	Evidence Review F	21	2 - 3	The evidence reports that no evidence available on repeat surgery. This does not mean that there are no benefits. Why is there no evidence? Why has there been no research done on patients within this group?	Thank you for your comment. NICE guidelines prioritise evidence from randomised controlled trials, as these are viewed as of the highest quality for questions on interventions due to their rigorous design that makes them the least susceptible to bias. Where no RCT evidence was available or when RCTs are not the most appropriate study design to answer the question, the committee considered non-randomised evidence/ lower quality evidence a priori on a question-by-question basis. However lack of evidence does not suggest that there are no benefits with repeat surgery. The committee agreed from their collective experience that input from a multidisciplinary team at a specialist centre should be sought, noting that repeat parathyroid surgery is relatively uncommon; failure rates are higher than in primary surgery and it carries a higher risk (recommendation 1.4.12). As there was a lack of sufficient evidence in this area, they also made a recommendation for future research on management after unsuccessful primary surgery.

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Hyperparathyroid UK Action 4 Change	Evidence Review G	5	19	Table 1 PICO characteristics of review question. Normocalcemic PHPT is mentioned in this table yet is elusive throughout the main guideline for what reason?	Thank you for your comment. We did not identify any evidence that met our protocol criteria specifically for people with normocalcaemic PHPT. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above. We found no substantive objective data on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B. Any future updates of this guideline will incorporate new evidence on normocalcaemic PHPT when it becomes available.
Hyperparathyroid UK Action 4 Change	Evidence Review G	6	11 - 15	*'In the other two studies, the minimum levels of serum calcium set for inclusion were lower (2.53 mmol/litre in Peacock 200519 and 2.62mmol/litre in Shoback 200325). The reference range for adjusted serum calcium is 2.2 to 2.6 mmol/litre. Therefore, all studies included people with hypercalcaemia and were analysed together**. No studies were identified for the results strata of normocalcaemic PHPT***. The last sentence is a contradiction of the first sentence….*' included lower levels of 2.53mmol/litre…'*	Thank you for your comment. The majority of the population across studies were hypercalcaemic and we were not able to distinguish between what is likely to be a very small proportion of people with serum calcium levels within the reference range hence results were analysed together.
Hyperparathyroid UK Action 4 Change	Evidence Review I	8	25 - 26	*The terms mild and non-mild in our opinions are not relevant to primary hyperparathyroidism. We don't hear the term mild pregnancy or mild cancer. We hear trimesters or stages. Primary hyperparathyroidism is a progressive disease. We have experience and case studies for people who have had the disease 2 years to*	Thank you for your comment. The terms mild and non-mild disease have been used in the papers included in the evidence reviews. We have not used these terminologies in our recommendations. We have referred to PHPT as a progressive disease in the committee discussion section of the evidence reviews.

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				over 30 years. The level of calcium does not depict the severity of this disease. The length of time a person has had primary hyperparathyroidism has more bearing. We have members who have levels barely above the population reference range who do not have kidney stones or fractures and would be classed by their endocrinologist as having 'mild' hyperparathyroidism consequently, yet they have had symptoms you class as non differential between 5-10 years or more, they have been unable to work, they have had breast cancer pancreatitis, tumours in their womb; all serious consequences of untreated primary hyperparathyroidism. We recommend you to include in this guideline that Primary Hyperparathyroidism is a progressive disease and by the time a person is presenting with debilitating symptoms, they may well have had PHPT a long time without them or their doctors knowing and surgery should be recommended to halt any further progression of the disease.	
Hyperparathyroid UK Action 4 Change	Evidence Review I	9	7 - 8	*We would like to dispute 'No evidence was available for people on calcimimetics, bisphosphonates and normocalcaemic patients'.* We understand one of your committee members was a lead writer on your calcimimetics guideline. Surely that guideline was evidence based? If we, the patients can find evidence and indeed provide evidence from our own clinical records, surely the committee is also able to find that evidence? Throughout our comments we have provided plenty of evidence regarding normocalcemic primary hyperparathyroidism, and are happy to	Thank you for your comment. The guideline was developed in accordance with the NICE guidelines manual (2014). NICE guidelines prioritise evidence from randomised controlled trials, as these are viewed as of the highest quality for questions on interventions due to their rigorous design that makes them the least susceptible to bias. Where no RCT evidence was available, the committee considered to look at non-randomised evidence/lower quality evidence a priori on a question-by- question basis. The details of this can be found in the protocols in appendix A of the evidence reports. The same principles applied throughout whereby the

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				assist your research team in finding evidence and knowing where to look for it. Please look at this study: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3474620/?fbclid=IwAR2IiWTuxn62eiSbkTfxW0f7NtP6hEneRvr-CaA7i9ExFjsqNMJytMjryYc#!po=0.819672	committee considered that lower quality evidence was more likely to be unreliable and therefore may not assist in making recommendations. The committee considered that performing a systematic review of all lower quality studies would have taken a huge amount of resource and would not have assisted in decision making. In areas where no clinical evidence was identified, the committee used their collective experience to make consensus recommendations. The committee was comprised of people with knowledge and experience of the primary hyperparathyroidism. How the committee made the recommendations is captured in the committee's discussion of the evidence in the evidence reports and in the rational and impact sections of the short guideline. The committee also identified areas where evidence to answer their review questions was lacking and have used this information to formulate recommendations for future research. The reference is an article examining the impact of treatment on asymptomatic PHPT and we have already included some studies in our reviews from the article which have met our protocol criteria.
Hyperparathyroid UK Action 4 Change	Research 3	General	General	Long-term outcomes of the different management strategies, I agree whole-heartedly that is important: quality of life measures, as well as other complications like bone density problems, renal and cardiovascular disease	Thank you for your comment.
Hypopara UK	Guideline	General	General	Consideration should be given to implementing routine serum calcium testing in the presence of vague and/or debilitating symptoms. Some patients suffer for months or years before GPs	Thank you for your comment. Routine testing of calcium was not raised during the scoping process of this guideline. Recommendations were made on testing people with signs and symptoms as this

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				think about testing serum calcium. Routine testing would be more cost effective in the longer term as it would identify the disease earlier.	represents the majority of people with primary hyperparathyroidism. Population screening for primary hyperparathyroidism was outside of the scope of this guideline.
Hypopara UK	Guideline	General	General	Many patients are still subjected to 'wait and watch' monitoring in the absence of positive imaging by many endocrinologists, even with a biochemistry clearly pointing to pHPT. We would ask that recommendations are made to refer these patients to an endocrine surgeon in a timely fashion to avoid the abject misery of those caught up in a pointless protocol.	Thank you for your comment. The committee were aware that people are being made to wait. We have made a recommendation (1.4.4) to consider referring someone for surgery regardless of pre-operative results. This recommendation will ensure that people have more timely access to surgery.
Hypopara UK	Guideline	3	7	We strongly feel that a comprehensive list of symptoms should be included here to aid diagnosis and ensure pHPT is not overlooked. A substantive poll of our members found the ten most common symptoms to be: *1 fatigue* *2 brain fog* *3 bone pain* *4 anxiety/depression/low mood/lack of enthusiasm in life* *5 muscle/joint pain* *6 irritability* *7 frequent urination* *8 increased thirst* *9 digestive problems eg GERD* *10 insomnia*	Thank you for your comment. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have amended recommendation 1.1.2 to be inclusive of all non-differentiated symptoms associated with PHPT. We have removed the examples of symptoms from recommendation 1.1.2 and now list the common symptoms in the section 'terms used in this guideline' and in the committee's discussion of the evidence in evidence report A in accordance with your list.
Hypopara UK	Guideline	4	11	The term 'hyperparathyroidism is suspected' is not useful. pHPT is often not suspected at primary level and we find that diagnosis often has to be patient- led. We suggest '*patient is symptomatic (see list above) or other tests support diagnosis.'*	Thank you for your comment. The recommendations do not preclude the patient raising the possibility of PHPT as a diagnosis with the GP. We have avoided the term symptomatic as it is now known that many people are unaware that the symptoms they are experiencing could be due to a diagnosable condition.

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Hypopara UK	Guideline	4	15	Suggest amend to '*Refer to specialist care if*:' Then immediate referral should be made to an endocrinologist or endocrine surgeon. (This needs clarifying as there is often confusion about referrals at primary level. We find most people diagnosed with, or suspected of, pHPT benefit by direct referral to an endocrine surgeon to avoid onset of, or deterioration of, known comorbidities. But we recognize that some people require ongoing care from an endocrinologist.	Thank you for your comment. Recommendation 1.1.8 has been edited. The committee wanted to be permissive to allow different pathways; in some cases this will be a referral or in others a telephone conversation. We wanted to allow for people who do not want to be considered for referral for surgery.
Hypopara UK	Guideline	4	16	1st bullet point suggest amend 'pHPT suspected' to '*patient is symptomatic'*. Many GP's do not appear to suspect pHPT. We suggest a 3rd bullet point about normocalcaemic cases – how will they be identified under this guidance?	Thank you for your comment. The committee discussed at length normal physiological distributions of calcium. What is recommended (recommendation 1.1.4) may occasionally miss some normocalcaemic PHPT presentations, but on balance will identify most people. Some cases of normocalcaemia are covered by the recommendation on what to do when a person has an albumin-adjusted serum calcium of 2.5 mmol/litre or above (recommendation 1.1.4). People with chronic non-differentiated symptoms will also be identified through the implementation of recommendation 1.1.2. No substantive objective data was identified on people with calcium below the limits specified. We have expanded the section on normocalcaemia in the committee's discussion of the evidence in evidence report B.
Hypopara UK	Guideline	5	3	We suggest *' If short term Vitamin D replacement exacerbates symptoms discontinue and consider early referral for surgery'* (We have noted that Vitamin D replacement can severely increase	Thank you for your comment. We recognise the importance of correcting vitamin D deficiency, but for some primary care providers vitamin D testing is not available. This would slow down referrals from primary care, and can therefore be done in secondary care.

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				hypercalcaemic symptoms with detrimental affect to quality of life.). Also vitamin D testing is sometimes difficult to obtain in primary care.	The committee discussed that Vitamin D can affect the interpretation of the urinary calcium test, hence in people who are vitamin D deficient, the specialist should interpret the urine calcium with caution. However the likelihood of a urine calcium result being low is highly unlikely and the committee agreed this should not be a major feature of the diagnostic algorithm but when urine calcium is low, rarely, there is a major focus on ensuring vitamin D repletion. We have edited the committee's discussion of the evidence in Evidence report B to include this detail.
Hypopara UK	Guideline	5	11	We suggest amend to 'Assessment by *specialist* after diagnosis'.	Thank you for your comment. The recommendations refer to specialists.
Hypopara UK	Guideline	5	21	We suggest amend to 'Refer people *directly* to a surgeon with expertise in parathyroid surgery if…'	Thank you for your comment. We discussed this with the NICE editor and we agreed that the current wording does imply a direct referral.
Hypopara UK	Guideline	5	22	'Surgeon with *expertise* in parathyroid surgery'. We feel this needs to be more clearly defined. Should BAETS suggest numbers?	Thank you for your comment. It is outside of the remit of this guideline to define what expertise a surgeon should have.
Hypopara UK	Guideline	5	23	Again – this should reflect the most commonly reported symptoms for reasons given above in note 1.1.1	Thank you for your comment. Recommendation 1.1.1 covers the most common presentations of PHPT which are the symptoms of hypercalcaemia. The committee recognised that people with primary hyperparathyroidism may experience a wide range of symptoms. We have amended recommendation 1.1.2 to be inclusive of all non-differentiated symptoms associated with PHPT. We now list the common symptoms in the section 'terms used in this guideline' and in the committee's discussion of the evidence in evidence report A to reflect those mentioned in your comment on the most common symptoms.
Hypopara UK	Guideline	5	26	Bullet point 3 – should consider stating serum calcium above range, or high normal with high	Thank you for your comment. The committee's definition of PHPT that is used in the guideline does

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				or high normal PTH. Those with normocalcaemic or normohormonal pHPT may slip through the net if serum calcium of 2.85 remains as the cut off level.	not preclude people with normal calcium or with mid-range PTH being diagnosed with PHPT.
Hypopara UK	Guideline	6	9 - 14	As the purpose is to help guide the surgery, would a less prescriptive and more generic guidance be more useful here as surgical units will already have a locally agreed protocol ?	Thank you for your comment. Based on evidence the committee agreed that for first-time surgery, the first pre-operative imaging would usually be ultrasound scanning as it is widely available, safe and does not involve any exposure to radiation. However, they noted that the accuracy of ultrasound depends on the expertise of the person performing it and ideally should be performed by a practitioner with expertise in head and neck imaging. They therefore allowed for sestamibi to be used if the expertise is not available to perform ultrasound. Sestamibi was proposed as a second option to ultrasound reflecting that its potential contribution outweighs its disadvantages compared to ultrasound in terms of additional cost and exposure to radiation. The committee noted that most centres use sestamibi, however some centres do use 4DCT. The committee from their knowledge and experience considered that the performance and radiation dose exposure for 4DCT and sestamibi were similar. The committee discussed the value of 4DCT but due to lack of evidence did not make a specific recommendation for this technique. Our recommendations are permissive around the second imaging modality, in line with the evidence reviewed. We have been prescriptive about one ionising radiation test for safety reasons.
Hypopara UK	Guideline	7	2	We strongly disagree. We feel that intraoperative monitoring should be used –	Thank you for your comment. The committee considered that there was not sufficient evidence to

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				there is evidence to support it, particularly in focussed or unilateral surgery, and this is in contrast to ESES guidance. It is used widely in Scandinavia, for example. Importantly, data from the UK Registry of Endocrine and Thyroid Surgery (www.baets.org.uk/audit) shows that post operative hypocalcaemia rates can reach 27%. 7-10% of cases still lead to permanent post- surgical hypoparathyroidism which IOPTH can help to avoid. As acknowledged, (p17) if diagnostic testing and surgery are cost effective treatments when resulting in a cure, so too is IOPTH, especially when further surgery or a lifelong condition can be avoided.	recommend IOPTH for first-time surgery. The committee from their knowledge and experience stated that there was a marginal benefit (0.9%-1.4%) with the use of IOPTH but debated if this was significant. They also noted that this marginal benefit could be partially attributed to surgical expertise. An exploratory cost effectiveness threshold analysis was undertaken for the use of IOPTH, which suggested that due to the high cost of testing and the very small marginal gain of using IOPTH as a result of the already high rates of successful surgery, IOPTH is highly unlikely to be cost effective at the NICE £20,000 per QALY gained threshold.
Hypopara UK	Guideline	7	4	There is no mention of what to do if patient is hypocalcaemic or symptomatic after surgery. There needs to be a clear protocol to avoid crises.	Thank you for your comment. The management of hypocalcaemia was not prioritised during the scoping process of the guideline.
Hypopara UK	Guideline	7	10	We disagree with 'do not routinely monitor'. Table 1 is less explicit. Annual calcium checks (at primary care) is the recommended practice in many centres and given the long term 5-10% risk or recurrent disease after 1 gland excision, the suggestion that patients should not be routinely monitored is of concern.	Thank you for your comment. The committee did not recognise 5-10% recurrence rates from PHPT curative surgery. We have amended recommendation 1.4.11 to monitor calcium no more frequently than once a year in people who have had successful surgery instead of only when a blood test is being taken for another reason.
Hypopara UK	Guideline	8	6	We feel that the cut off level for Cinacalcet should be set lower based on the known fact that there is no correlation between severity of symptoms and level of serum calcium. Many patients with serum calcium lower than 2.85 suffer severely debilitating symptoms and could benefit from Cinacalcet.(p23 line 2)	Thank you for your comment. Cinacalcet acts to decrease serum calcium and therefore the committee considered the largest benefit would be in people with an adjusted serum calcium level above the reference range. Therefore, most benefit will be achieved in people with a high serum calcium level and symptoms resulting from their hypercalcaemia. It would also lower the risk of end organ damage.
Hypopara UK	Guideline	9	4	We think there also needs to be a clear protocol for patients who are symptomatic or	Thank you for your comment. The management of hypocalcaemia was not prioritised during the scoping

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				hypocalcaemic post surgery (and not listed in Table 1) to avoid crises. They would need frequent monitoring and referral to an endocrinologist.Does 'unsuccessful' include them?	process of the guideline.
Hypopara UK	Guideline	10	3	Also consider preconceptual care.	Thank you for your comment. Recommendation 1.7.1 'Offer parathyroid surgery to women who have primary hyperparathyroidism and are considering pregnancy' covers preconceptual care.
Hypopara UK	Guideline	10	3	In diagnosis in pregnancy, use ionized calcium test to diagnose pHPT in pregnancy due to low albumin?	Thank you for your comment. In the experience of the committee it is not necessary to measure ionised calcium. They discussed that ionised calcium testing cannot be done in primary care and it would usually be undertaken using a blood gas analyser in hospital. They considered that as ionised calcium measurement is a point-of-care test it is not subject to stringent quality control like laboratory- based tests. Furthermore the sample has to be handled very quickly, making it a less reliable test.
Hypopara UK	Guideline	10	6	6 (12,13) If this recommended MDT is not practical (which with current staffing levels it probably isn't) all parties need to be made aware of the care plan which should detail the specialised needs of mother and baby. Ensure care plan is in place.	Thank you for your comment. We have added your suggestion to the committee's discussion of the evidence in evidence report J.
Hypopara UK	Guideline	10	14	Cinacalcet may occasionally be needed when surgery is not practical (too advanced pregnancy or mediastinal glands or failed surgery) so should not be recommended against.	Thank you for your comment. The recommendations are for people in whom surgery is unsuitable.
Hypopara UK	Guideline	10	22	We feel that monitoring should be carried out every two weeks during pregnancy and 3 months after to ensure patient safety. (P26 line 16) Needs will also change during	Thank you for your comment. Based on their experience the committee agreed that in pregnant women with PHPT, monitoring strategies and frequency should be tailored based on individual

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				breastfeeding.	patient assessment and determined by advice from a specialist multidisciplinary team. No evidence was identified on breastfeeding and the committee were unable to make any recommendations on it.
Hypopara UK	Guideline	11	2, 5	A considerably different approach is required to advise those planning for a baby (see comments 17 and 23) and those who are already pregnant. For the latter, there is an ethical problem here – reassurance is important but there are risks so shouldn't mother be told?	Thank you for your comment. The benefits and risks of any treatment would be discussed with the mother.
Hypopara UK	Guideline	11	12	Please recommend and supply links to Hypopara UK leaflet on Primary Hyperparathyroidism (BMA highly commended) and to their website for information and support www.hypopara.org.uk. (New website launching soon.)	Thank you for your comment. We are unable to signpost to patient information leaflets in the guideline. We have made the committee aware of the leaflet you mention.
Hypopara UK	Guideline	12 - 13	18	Further recommendations for research: exploring causes of failure in first time surgery, vitamin D replacement in pHPT, differentiating between single and multi gland disease, quantify patient led diagnosis, PTH testing, normocalcaemia and the need to try and predict multigland disease, pHPT in children.	Thank you for your comment. The committee has a made a recommendation for future research on management after unsuccessful primary surgery. The committee agreed these are important areas but some of the topics (vitamin D replacement in PHPT, differentiating between single and multi -gland disease, quantify patient led diagnosis, and the need to try and predict multi-gland disease, PHPT in children) were either not prioritised for a review question or are beyond the scope of this guideline.
Hypopara UK	Guideline	15	28	pHPT is not always discovered in routine blood tests and can be commonly discovered after patients who have been chronically	Thank you for your comment.

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				symptomatic insist on a calcium test.	
Hypopara UK	Guideline	16	10	Please refer to comment 5 above re Vitamin D	
Hypopara UK	Guideline	16	14	It is not always true that FHH requires no treatment. The literature suggests that in some cases surgery can be beneficial.	Thank you for your comment. The diagnosis and management of FHH was outside of the scope of this guideline
Hypopara UK	Guideline	17	8	Suggest use list at 1.1.1 to be more specific about the most commonly reported symptoms to increase awareness.	Thank you for your comment. We have amended the list of symptoms in the committee's discussion of the evidence in evidence report A to reflect those mentioned in your comment on the most common symptoms. These also now appear in the section 'terms used in this guideline'. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made a recommendation to offer an albumin-adjusted serum calcium test where such symptoms are present. Where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions we have recommended to consider testing. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.
Hypopara UK	Guideline	27	3	Recs 1.7.1 – 1.7.5 The committee makes a good point about informing patients but should seriously consider recommending more comprehensive education for HCPs at primary level in recognising and acting upon signs and	Thank you for your comment. We have passed your comment on to the NICE implementation team who work with organisations to help to put guidance into practice.

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				symptoms of pHPT	
Kingston Hospital NHS Foundation Trust	Guideline	4	16	We feel it would be helpful for primary care Physicians if it mentions after excluding/correcting Vitamin D deficiency	Thank you for your comment. The committee agreed that measuring vitamin D and correcting any deficiency is essential in treating people with primary hyperparathyroidism (see recommendation 1.2.1). We have edited the committee's discussion of the evidence in evidence report B to include this detail.
Kingston Hospital NHS Foundation Trust	Guideline	5	General	There is no emphasis on correcting Vitamin D deficiency before measuring urinary calcium as vitamin D deficiency can lead to lower urinary calcium excretion. Recommendation around interpreting urine calcium in patients with chronic kidney disease especially in the earlier stages would be appreciated.	Thank you for your comment. We do recommend that calcium should be taken at the same time as PTH (recommendation 1.1.6). The committee agreed that measuring vitamin D and correcting any deficiency is essential in diagnosing and treating people with primary hyperparathyroidism, but noted that correcting a deficiency does not need to precede the diagnosis. The committee recognises the importance of correcting vitamin D deficiency, but for some primary care providers vitamin D testing is not available. This would slow down referrals from primary care, and can therefore be done in secondary care. The committee discussed that Vitamin D can affect the interpretation of the urinary calcium test, hence in people who are vitamin D deficient, the specialist should interpret the urine calcium with caution. However the likelihood of a urine calcium result being low is highly unlikely and the committee agreed this should not be a major feature of the diagnostic algorithm but when urine calcium is low, rarely, there is a major focus on ensuring vitamin D repletion. We have edited the committee's discussion of the evidence in evidence report B to include this detail.
Kingston Hospital NHS Foundation Trust	Guideline	6	13 - 14	While we appreciate the logic for limiting imaging to two modalities, in our experience	Thank you for your comment.

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				CT parathyroid protocol by dedicated head and neck radiologist has been very helpful in identifying adenoma thereby facilitating focused parathyroidectomy	
Kingston Hospital NHS Foundation Trust	Guideline	6	18 - 19	We feel this could be reworded. It makes it sound as if patients should be made to choose between 4-gland explorations versus focused parathyroidectomy in the context of image positive solitary adenomas. Instead, the statement should acknowledge that for first time surgery, depending on local surgical expertise, consideration should be given to either a focused parathyroidectomy or 4-gland exploration given that there is good data to show the cure rates are similar (>95%). Instead emphasis should be placed on the pros and cons of either surgical approach being discussed with patients.	Thank you for your comment. We do recommend that people are still given the choice of what surgery to opt for even when the imaging shows a single adenoma. We have added that benefits and risks should be discussed to recommendation 1.4.6 and the areas on which information should be given.
NHS England	Guideline	General	General	**General initial comments** Comments are in regard to the initial diagnosis and referral, from a primary care perspective, as a GP. Firstly the guidance for the initial assessment and tests requested are not that much different to what is current practice so in response to the initial questions 1-3 above the answers are "no". But I cannot comment on these questions with regard to the surgical and subsequent management**.**	Thank you for your comment.
NHS England	Guideline	General	General	**General on points of interest in guidance.** The overall guidance is common sense and my impression is that this is currently usual	Thank you for your comment. The guideline committee discussed the setting of the urinary calcium test. Due to the committee's experience of difficulties in primary care in obtaining correctly timed collections and with

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				practice. I would also say that checking bone profile (but not PTH) is usual when investigation fatigue/tired symptoms as rarely hypercalcaemia can be the cause. I would make some suggestions on pre-referral investigations though, but this may depend on how proactive the GP is. The tests recommended after diagnosis include Renal USS, DEXA and possibly 24hr urinary calcium. I wonder if the urinary calcium should be included before referral, although 78 times less common than primary hyperparathyroidism I would expect secondary care to request this when they see the patient (it may save a further OPD appointment to review with results if the results are already available when initially seen). The test is cheap and easily available. I agree the Renal USS/DEXA can wait until after diagnosis.	collections being made in the incorrect container, secondary care was considered to be the appropriate setting for this test. The committee also did not want to slow down referrals or discussions with secondary care specialists and initiating this test in primary care would add a barrier to timely referral. This information has been added to the committee's discussion of the evidence in evidence report B.
NHS England	Guideline	General	General	Specific questions asked to comment on **To the best of your knowledge, how widely adopted is this quality standard in the NHS currently. E.g. a small number of early adopters/fairly widespread etc.** My impression is that the current approach is widely adopted. I can comment on a recent case myself where I picked up al hypercalcaemia on checking blood tests	Thank you for your comment. The committee agreed and reflected in the recommendations the action to be taken if PTH is below the midpoint of the reference range and albumin-adjusted serum calcium is 2.6 mmol/litre or above. The committee's recommendations reflect that it is the combination of calcium and PTH that is important.

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				following presentation with fatigue. Unknowingly I followed the guidance currently recommended since it seems intuitive and common-sense. I would expect my GP colleagues to act in the similar manner. Less widely known is that the PTH does not need to be outside the normal upper range to be high so I would suggest emphasis of this in further guidelines.	
NHS England	Guideline	General	General	Specific questions asked to comment on **To the best of your knowledge, what would you consider to be the biggest barrier/s to commissioning and/or adoption of this quality standard.** Again from a primary care perspective it isn't very different to current practice so would not anticipate problems or barriers.	Thank you for your comment.
NHS England	Guideline	General	General	Specific questions asked to comment on **To the best of your knowledge, and broadly speaking, which (if any) of the recommendations might require additional funding or workforce to deliver, and why.** Again from a primary care perspective it isn't very different to current practice so would not anticipate needing additional funding/workforce	Thank you for your comment.
NHS England	Guideline	General	General	Ultrasound is undertaken by sonographers who are currently not regulated and radiographers and radiologists who are, consideration will be required to ensure dissemination of any training required to meet this guideline across all staff groups.	Thank you for your comment. The committee acknowledged the variation in clinicians performing ultrasound and discussed that the accuracy of ultrasound depends on the expertise of the person performing it. The committee agreed that the ultrasound should be

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					performed by a practitioner with expertise in head and neck imaging but. acknowledged the current shortage of practitioners with this expertise. To address this the committee recommended a sestamibi scan if it would further guide the surgical approach.
NHS England	Guideline	3	5	"1.1.2 Do not measure ionised calcium when testing for primary hyperparathyroidism." There is reported variation in UK laboratories on calcium measurements. There may need to be a consensus agreement on standardising calcium measurement methodology. There may be implications for primary care where commissioners are introducing point of care testing.	Thank you for your comment. Individual laboratories decide how to measure calcium and it is not within our remit to specify which one they should use.
NHS England	Guideline	19	17	The guideline details that ultrasound should be performed by a specialist head and neck radiologist, however dependent on the information contained in the investigation request, the procedure may be performed in practice by a sonographer. Some sonographers are developing expertise in this field. If subsequent ultrasound guided intervention is required this should be completed with the support of a radiologist.	Thank you for your comment. The committee discussed that the accuracy of ultrasound depends on the expertise of the person performing it and ideally should be performed by a practitioner with expertise in head and neck imaging. They therefore allowed for sestamibi to be used if the expertise is not available to perform ultrasound. In the committee's discussion of the evidence we refer to ultrasound being conducted by a radiologist.
NICE GP Reference Panel	Guideline	General	General	The GP Reference Panel was asked to provide comments on this draft guideline. They had not contributed comments previously (e.g. during scoping) We asked them to focus particularly on Section 1.1 (diagnosis and assessment) and 1.5	Thank you for your comment.

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				(monitoring) as these seemed most relevant to primary care. They were also invited to make comments on other sections if they wished. Replies were received from 10 panel members. Unedited comments are listed below and numbered 1-10 for reference. In keeping with previous reference panel feedback, I have summarised member's comments and attach their unedited comments in the final line with numbers for reference. JT	
NICE GP Reference Panel	Guideline	General	General	2 respondents (2+8) were happy with the draft without suggestions for change.	Thank you for your comment.
NICE GP Reference Panel	Guideline	General	General	**Unedited GP reference Panel member responses** **Response 1** 1. It appears therapy, largely surgical occurs at calcium sustained at 2.85 or higher but that referral should occur above 2.6 I have had 2-3 older women over 30 years, with comorbidities and no symptoms that all low asymptomatic hyperparathyroid patients should be referred or can GPs be asked to monitor? Would it be reasonable to ask GPs to use judgement with patients about comorbidity, function and life exectancy before recommending neck surgery? 2. I was not clear how bloods and urinary calcium would happen for the patient. It looked like the GP needed to take 2 calcium levels (at set interval) and then do a vit D, is the urinary calcium and the eGFR at the same time? Can	Response 1 Thank you for your comment. We have edited recommendation 1.1.8 to make it clearer that advice is being sought from a specialist with expertise in PHPT. There are different criteria for surgery. In the case you refer to (we assume aged 80) the recommendation allows for the GP to discuss but not refer. We have edited the heading of the recommendations for vitamin D and FHH to make it clear that these tests are in secondary care. We recognise that ALP would usually be part of bone profile testing but the committee do not think this is essential. The committee listened to the considerable, consistent patient voice (stakeholder comments on the scope and guideline) who feel they are not listened to and these

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				we rationalise how often and when patients attend the GP clinic as this also has a cost implication. Should an ALP be recommended as well to look at boney activity? 3. clear advice on follow up bloods and not overtesting is always welcome **Response 2** Useful guidance, gives clear protocol for when to repeat PTH and refer in primary care. **Response 3** much of this guideline refers to secondary care specialists. Section 1.1.4 gives an extremely wide and vague non-differentiated list of symptoms which at times could encompass the majority of my patient workload on any given day! How realistic is it to ask primary care to investigate with bloods each and every patient who presents with these vague constellation of symptoms. My fear is that this may result in a significant resource commitment for very few positive findings. **Response 4** my main comment would be that the monitoring table gives absolutely no guidance on how to act on results – I presume it is assumed we would refer back every patient with an albumin- adjusted calcium above 2.6 and raised PTH as per initial referral guidance but I think this could be much clearer. I don't find this adds much to primary care management	recommendations will direct them towards the most appropriate first test. Some stakeholders reported that people are having vitamin D as a first-line test which is inappropriate. Calcium is the most appropriate first test for suspicion on PHPT. Response 2 Thank you for your comment. Response 3 Thank you for your comment. Recommendation 1.1.1 is based on symptoms with a strong association with hypercalcaemia. A consider recommendation (1.1.2) is made for other symptoms where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions but we recognise that clinical judgement should be used when deciding if it is appropriate to test for calcium. This guideline does not replace clinical judgement. Response 4 Thank you for your comment. We have edited the table to direct people to the recommendations (actions) that should be taken following a positive monitoring test.

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				Response 5 1.1.1 slightly oddly says measure calcium if you have found the calcium to be raised. What this means I think is don't act on single isolated raised calcium but that you need to confirm 1st. 1.1.3 Making the distinction between 2.5 and 2.6 is likely to cause more confusion than it is to solve problems. Why not agree on 2.5? Quote "fatigue might indicate raised PTH and so consider testing Ca" could be replaced with measure calcium if investigating fatigue symptoms. That would be clear and to the point. Saying might be and consider doing is less helpful. 1.1.6 some (maybe all) labs do not do PTH testing on community samples but want them taken close to a centrifuge for prompt spinning down. ?Add something to say check local protocol for PTH testing. Nil to add on the monitoring section	Response 5 Thank you for your comment. It is important to distinguish between people with an albumin-adjusted serum calcium of 2.5 mmol/litre and 2.6 mmol/litre. There is a group of people who are symptomatic but have a calcium level in the high end of the normal range. It is important to test for PHPT in people with a higher calcium irrespective of symptoms because of the strong association between the two. The recommendation on fatigue is to test for calcium and not PTH. The handling of blood samples was not prioritised during the scoping process of this guideline.
				Response 6 it seems reasonably clear except do i use a bisphosphonate or not or do they mean only if have evidence of osteoporosis as well and eligible when do you refer to a endocrinologist ie	Response 6 Thank you for your comment. We consider overarching fracture risk, including bone density, to determine management strategy. Hence the committee agreed that bisphosphonate treatment could be considered as a means of reducing fracture risk for people with primary hyperparathyroidism and increased fracture

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				calcium levels above 3.0 or very high levels what do you do if your local lab won't let you check vit D levels but you have to refer for this? **Response 7** These recommendations would significantly increase the amount of testing done in primary care. In particular the recommendation in 1.1.1 to test in constipation and 1.1.4. to test with symptoms of fatigue or depression. These are very common presentations in primary care. It is noted in lines 24-25 on page 14 that "...there is uncertainty about the relationship between these symptoms and primary hyperparathyroidism". If there is no good evidence to be testing, it should not be recommended. Testing is increasing at an alarming rate in primary care, and we should be mindful of the harms done by over-testing. **Response 8** No comments from a primary care perspective.	risk. The committee based the recommendation on the NICE technology appraisal guidance on bisphosphonates for treating osteoporosis. The threshold for calcium is for PTH testing and the PTH thresholds are to seek advice from a specialist with expertise in primary hyperparathyroidism. We have edited the heading for the vitamin D recommendation to make it clearer. Response 7 Thank you for your comment. Some symptoms are most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made an 'offer' recommendation based on these. A 'consider' recommendation is made for other symptoms where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain. Response 8 Thank you for your comment.

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				Response 9 Section 1.1 I am somewhat confused here. We GPs have previously referred patients with suspected hyperparathyroidism to the Endocrine service-are Nice now suggesting that all this pre surgical assessment is done by GPs? It is going to be hard to remember all this and need a lot of appointments to follow up all the different stages of investigation. I do not routinely check calcium in all patients with a new diagnosis of osteoporosis -I was unaware this was necessary-so this would mean basically checking all our elderly female patients as those with high risk scores now often get treated rather than having formal Dexa scans etc. What is the clinical yield from checking calcium in this group? If I am checking bloods for a tired all the time screen I do not usually include a calcium-these days we are more likely to send a vitamin D level in these patients. Section 1.1.8- ' if PTH is above the mid point of the reference range and there are symptoms-consider surgical referral' - this is just too confusing-the PTH level is either in the normal range or it is not-this is for specialist interpretation in an endocrine clinic-it is just not going to work for non-specialists. I think Nice need to make it clear who this guidance is for-I would feel this rare endocrine	Response 9 Thank you for your comment. We recommend checking calcium in people who have symptoms most robustly associated with hypercalcaemia of primary hyperparathyroidism and we have therefore made an 'offer' recommendation based on these. A 'consider' recommendation is made for other symptoms where there is not such a strong association with PHPT or the symptoms could indicate a number of different conditions. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain. We recommend checking calcium in people with osteoporosis. Older people with PHPT may benefit from surgery and need to be considered for it. Calcium is the most appropriate first test for suspicion of PHPT. A 'consider' recommendation is made for checking calcium in people with fatigue. The committee have carefully considered the recommendations on PTH and in their knowledge and experience consider them to be clear, and highlight that both symptoms and PTH need to be taken into consideration in decision making. We have discussed this in the rationale and in the committee discussion section of Evidence report B. Please also see algorithm 1.

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				condition would be better managed in secondary care-perhaps by a clinical nurse specialist. If this is going to be transferred to GPs then we would need a very straightforward flow chart to follow, otherwise these patients are not going to get the assessment and monitoring they deserve. **Response 10** Is the differentiation between levels of 2.5 and 2.6 (sections 1.1.3 and 1.1.5) really significant? It makes the guideline more complicated and confusing than it needs to be (unless there's strong evidence). Should be easy to remember the level that needs to be investigated. 1.1.4 seems reasonable - I think most people would check bone chemistry as part of a screen in this situation. Not quite sure of the rationale for 1.1.8, it would be helpful to have this explained in the guidance. 1.1.10 could include more examples of differential diagnosis, eg sarcoid 1.1.11 could include advice on correcting deficiency or appropriate link 1.2.1 - I recently made this diagnosis in an 85yo lady, she is not being referred for surgery. Could this be reworded to something like consider (or offer) referral if clinically	Response 10 Thank you for your comment. We think the distinction between a calcium level of 2.5 mmol/litre and 2.6 mmol/litre is clear. The rationale for these thresholds can be found in the rationale section and the committee discussion section of evidence report B. The committee have carefully considered the recommendations on PTH and in their knowledge and experience consider them to be clear. The full committee discussion can be found in the rationale section and in committee discussion section of evidence report B. The committee agree that those with multigland disease will benefit from a specialist with knowledge of associated syndromes. We anticipate that by reading this guideline health professionals will access high quality materials to supplement their knowledge of these syndromes. The management of Vitamin D deficiency was outside of the scope of this guideline. We have edited recommendation 1.3.2 to make the distinction with 1.3.1 clearer. We have also edited recommendation 1.4.6 to make it clear that the benefits

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				appropriate. 1.2.1 and 1.2.2 - these two conflicting pieces of advice aren't particularly helpful. One or the other. Rationale and impact section didn't really clear it up. 1.4.4 and 1.4.5 - distinction needs to be made clearer between these two scenarios 1.5 Table 1. Guidance stating 'consider' in the context of monitoring advice is unhelpful. In middle box of bottom line the wording is unclear ('at diagnosis and when presenting'). The third column could instead be presented as a comment after the table, this would allow the other two columns to be wider for improved clarity.	and risk of surgery should be discussed with the person. We have edited recommendations 1.5.4 and 1.5.5 to make them clearer. We have edited the monitoring table in section 1.6 to make it clearer.
NICE GP Reference Panel	Guideline	3	5	1.1.1 One respondent (5) was confused by the final bullet point which was interpreted as making a point about RE-testing	Thank you for your comment. People who had a high calcium on an incidental blood test would have their albumin-adjusted serum calcium retested.
NICE GP Reference Panel	Guideline	3	17	1.1.3 Two respondents (5+10) found the distinction between Calcium of 2.5 and 2.6 confusing and wondered if it was necessary.	Thank you for your comment. The committee discussed that it would not be cost effective to check everyone with an albumin-adjusted serum calcium of 2.5 mmol/litre and people with this level should be tested in the presence of symptoms. Due to the risks associated with a level of 2.6 mmol/litre or above these people should be tested irrespective of symptoms. Also, the committee stated 2.6 mmol/litre because it is an incidental finding rather than in people presenting to the GP with symptoms.
NICE GP Reference Panel	Guideline	4	3	1.1.4 Four respondents (3,5,7+9) expressed concern	Thank you for your comment. We have now edited recommendation 1.1.2 to make it clearer.

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				at the perceived recommendation to test for Calcium for very common symptoms. I think this reflects a lack of understanding of the "Be aware…" term. Perhaps it could be made clearer that GPs are not being asked to always test for Calcium when any of these symptoms present. Respondent 5 makes a valuable comment about the language used with regard to fatigue. Respondent 7 mentions constipation in particular. It is mentioned in section 1.1.1 as an "or". Perhaps it would sit better in section 1.1.4 If constipation needs to be included in section 1.1.1, then perhaps it should be made clear that this is part of a symptom cluster (an AND not an OR).	Recommendation 1.1.1 is based on symptoms with a strong association with hypercalcaemia but we recognise that clinical judgement should be used when deciding if it is appropriate to test for calcium. The symptoms can be present in isolation.
NICE GP Reference Panel	Guideline	4	7	1.1.5 One respondent (10) mentioned the Calcium 2.5 and 2.6 separation as confusing. One respondent (5) mentioned that PTH testing has to be done in hospital to allow rapid testing (an important practical point) 2 respondents (9+10) found the mid-point-of-reference-range advice (1.1.8 and 1.1.9) confusing.	Thank you for your comment. The committee discussed that it would not be cost effective to check everyone with an albumin-adjusted serum calcium of 2.5 mmol/litre and people with this level should be tested in the presence of symptoms. Due to the risks associated with a level of 2.6 mmol/litre or above these people should be tested irrespective of symptoms. In the knowledge and experience of the committee PTH can be measured in primary care. Ionised calcium requires rapid testing. It is necessary to refer to the reference range in order to make sure people are correctly diagnosed.
NICE GP Reference Panel	Guideline	4	14	1.1.7 One respondent (1) appreciated this negative	Thank you for your comment.

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				recommendation not to repeat test PTH.	
NICE GP Reference Panel	Guideline	5	2	1.1.11 One respondent (10) suggested including or linking to advice on managing abnormal vitamin D levels.	Thank you for your comment. The NICE guideline on vitamin D deficiency (PH56) does not make any recommendations on managing vitamin D deficiency.
NICE GP Reference Panel	Guideline	5	5	1.1.12 One respondent (1) commented on urine calcium excretion testing. At what point should this be done? AFTER we have a raised PTH? These are complicated tests which we would want to keep to a minimum in primary care. Should an ALP be included at some point?	Thank you for your comment. We have edited the heading of the section for excluding familial hypocalciuric hypercalcaemia to make it clear this is done in secondary care. We recognise that ALP would usually be part of bone profile testing.
NICE GP Reference Panel	Guideline	5	20	1.2 Two respondents (1+10) questioned the threshold for referral for patients who may not be good surgical candidates. One respondent (6) seems to have missed the specialist referral recommendations One respondent (10) found 1.2.1 and 1.2.2 contradictory.	Thank you for your comment. We have edited recommendation 1.4.6 to make it clear that the benefits and risk of surgery should be discussed with the person. We have edited 1.3.2 to make the distinction with 1.3.1 clearer.
NICE GP Reference Panel	Guideline	8	1	1.4 Two respondents (6+10) were confused by this section. I think what the guideline is trying to say is : "Don't use a long term bisphosphonate to try and manage hypercalcaemia, BUT if a patient has osteoporosis, it's OK to treat that condition with a bisphosphonate even if they have	Thank you for your comment. We have edited recommendation 1.5.5 to make it clearer. The committee discussed that bisphosphonates do not reduce hypercalcaemia in the long term and should not be offered for management of chronic hypercalcaemia of PHPT. There was evidence showing that bisphosphonate treatment improves lumbar spine bone mineral density for people with primary hyperparathyroidism. Based on the evidence and their

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				primary hyperparathyroidism."	experience, the committee agreed that bisphosphonate treatment could be considered as a means of reducing fracture risk in this group of patients. We consider overarching fracture risk, including bone density, to determine management strategy.
NICE GP Reference Panel	Guideline	9	1	1.5 One respondent (4) requested that the table includes how to respond to abnormal results if they arise as a result of monitoring. One respondent (10) felt the use of the word "consider" was not helpful in this context. My interpretation of this comment is that they feel that if something needs monitoring it either does or it doesn't. If there are situations when monitoring is NOT necessary, then the guideline should be clear about when this is - on what do we base our consideration? They also found the language about renal USS unclear ("at diagnosis and when presenting"). They also suggested that column 3 could be removed to allow more space and the comment in here made as a foot note.	Thank you for your comment. We have edited the table to direct people to the recommendations (actions) that should be taken given a positive monitoring test. Some recommendations are made with more certainty than others. The wording of the recommendations reflects this. For example we use 'offer' to reflect a strong recommendation, usually where there is clear evidence of benefit. We use 'consider' to reflect a recommendation for which the evidence of benefit is less certain. Due to the absence of evidence we were only able to make consider recommendations on monitoring. The committee agreed and have now edited the table to only include 'at diagnosis'.
Sheffield Teaching Hospitals NHS Foundation Trust	Guideline	General	General	It is suggested that two or more measurements of albumin adjusted serum calcium are made, but there is a requirement that both or all are high. We believe it is better to take the average calcium and if that is above 2.6, then consider the calcium high. It would be helpful to comment on the optimal number (say, three), the fasting status (non-fasting is adequate) and the period (at least one week apart, for example).	Thank you for your comment. The recommendations are in line with current practice and there was no evidence to support taking the average calcium. The recommendations are for two or more (if indicated) measurements of calcium to allow for individual variability around the assays. We explain in the committee's discussion of the evidence that a random sample is adequate. The interval between the tests was discussed by the committee but in the absence of evidence no consensus could be reached.

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Sheffield Teaching Hospitals NHS Foundation Trust	Guideline	3	18	The term "primary hyperparathyroidism is suspected" is very unclear. Does this mean that if the patient has thirst and a calcium of 2.5 that PHPT should be suspected? We wonder if NICE was considering the disorder 'normocalcaemic hyperparathyroidism'? If so, we would recommend leaving out the recommendation of a lower threshold for calcium and having a section about this disorder.	Thank you for your comment. The committee sought to capture people with an albumin-adjusted serum calcium in the high end of the normal range who have symptoms of hypercalcaemia. Recommendation 1.1.2 recommends that people with chronic non-differentiated symptoms are considered for calcium testing. There was recognition that normocalcaemic primary hyperparathyroidism is a relatively recent diagnosis and the natural history of the disease and its optimal management is still unclear. In light of above, the committee therefore agreed that setting a threshold for PTH measurement of albumin-adjusted serum calcium level repeatedly 2.6 mmol/litre or above, or 2.5 mmol/litre or above if there is clinical suspicion of hyperparathyroidism, would identify most people with primary hyperparathyroidism. The section on normocalcaemic primary hyperparathyroidism has been strengthened in the committee's discussion of the evidence in evidence report B.
Sheffield Teaching Hospitals NHS Foundation Trust	Guideline	3	19	Albumin adjusted serum calcium: There are several methods for adjusting calcium for albumin. The committee should make a recommendation since this is the key test for the guideline.	Thank you for your comment. The committee was aware that there are several equations for adjusting serum calcium, however each laboratory needs to take into account their methods for calcium and albumin and their population mean for those values rather than adopting a 'fixed' equation. Laboratories should regularly review what is happening to their correction calculation.
Sheffield Teaching Hospitals NHS Foundation Trust	Guideline	4 and 16	4 and 12	4 and 12 respectively Excluding Familial Hypocalciuric Hypercalcaemia: It isn't clear whether a 24-hour urine collection or a time fasting urine collection is recommended. The terms are not clear and would be helped by giving the units. Cut-offs should be given otherwise the tests	Thank you for your comment. We have edited the recommendations to specify random for renal calcium:creatinine excretion ratio and calcium:creatinine clearance ratio. Cut-offs for these tests are determined locally.

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				are of no help.	
Sheffield Teaching Hospitals NHS Foundation Trust	Guideline	4	15	When to refer for specialist advice. The options come across as confused as they don't include all circumstances. The algorithm 1 is much clearer.	Thank you for your comment. The guideline will clearly link to the algorithms.
Sheffield Teaching Hospitals NHS Foundation Trust	Guideline	6	1	Referral for surgery: This recommendation contradicts section 1.2.1. If the panel really believe this, then they should simply say send everyone with the diagnosis to the surgeon! It would be better to selective and just keep section 1.2.1. They might add an age indication (surgery for all patients less than 50 years).	Thank you for your comment. The committee was satisfied on the basis of the evidence that surgery is indicated for those in whom it is currently being performed, and for this group made an 'offer' recommendation. However they recognised that there is a case to be made for people who do not fall into these traditional criteria, and recommended these that patients should be considered for surgery. In the absence of evidence regarding age and surgical outcome and in accordance with the NICE equality policy age is not a criteria for surgery.
Sheffield Teaching Hospitals NHS Foundation Trust	Guideline	8	16	Section on bisphosphonates: It is recommended that the algorithm for osteoporosis is used to guide treatment. We usually recommend a drug holiday after 5 years in postmenopausal osteoporosis. Would this be recommended in PHPT? At the very least, this question should be on the research agenda.	Thank you for your comment. We cross refer to the NICE technology appraisals in recommendation 1.5.4.
Sheffield Teaching Hospitals NHS Foundation Trust	Guideline	9	Table 1	Monitoring people with PHPT. There is no consideration of what to do if any of the measurements change. How much bone loss would trigger action? How much of a change in serum calcium would trigger a recommendation for surgery? How variable are these measurements?	Thank you for your comment. In the absence of evidence the committee were unable to define the thresholds. However, a referral for surgery would be triggered in accordance with the criteria in 1.3.1 and 1.3.2. We have added the relevant recommendation to the table.
Sheffield Teaching Hospitals NHS Foundation Trust	Guideline	16	5	Section on Vitamin D: This is a very weak section. There is plenty of evidence about the prevalence of vitamin D deficiency and systematic reviews on the treatment with	Thank you for your comment. We are unable to summarise the evidence prepared in other guidelines about vitamin D and treatment unless they meet the criteria in our review protocols. The management of

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				vitamin D. The dose required to replete vitamin D needs to be given (high dose) and there is no need for supplemental calcium. Furthermore, PTH needs to be reassessed after repletion as the PTH might have been high simply as a result of secondary hyperparathyroidism.	vitamin D deficiency was outside of the scope of this guideline.
Sheffield Teaching Hospitals NHS Foundation Trust	Guideline	16	24	ALP: This is an inexpensive test, commonly done along with calcium and albumin. A high value might indicate osteitis fibrosa cystica and this would predispose to hungry bone syndrome and postoperative hypocalcaemia.	Thank you for your comment. The committee agreed that ALP would usually be part of bone profile testing.
Sheffield Teaching Hospitals NHS Foundation Trust	Guideline	18	7	Recommendation for surgery to treat non-specific symptoms: There have been several clinical trials for asymptomatic hyperparathyroidism and none of them have showed any benefit on quality of life measures. This statement cannot be justified based on evidence.	Thank you for your comment. The sentence reflects the evidence presented in evidence report E.
Sheffield Teaching Hospitals NHS Foundation Trust	Algorithm 1	General	General	eGFR measurement: This is being measured late in the course of the investigation. We need to know about eGFR early on.	Thank you for your comment. The committee recognises that measurement of renal function is important in assessing calcium and PTH levels. Most patients will have eGFR measured with serum calcium. An elevated serum calcium should be investigated irrespective of eGFR and the proposed algorithms are designed to ensure if eGFR has not been checked early in the diagnostic pathway, it is done so as part of the investigation and assessment of patients with hypercalcaemia.
Society For Endocrinology	Guideline	General	General	One member of our Clinical Committee commented: "The recommendation for US imaging to detect renal stones is picking an imaging modality with a much lower sensitivity and specificity than other techniques such as CT KUB. While it doesn't use radiation it will	Thank you for your comment. CT KUB was not specified by the committee in the protocol for this review and therefore we were not able to make recommendations on it.

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				miss a substantial number of kidney stones so potentially people who would meet the criteria for surgery could be missed. I know other guidelines have been less prescriptive on the technique used and I wonder if alternatives such as a CT KUB should be included due to its better sensitivity and specificity."	
Society For Endocrinology	Guideline	19	2	Line 2 onwards One member of our Clinical Committee commented: "I find the recommendation to only do US neck +/- sestamibi for localisation prior to surgery to look at all 4-glands interesting as they've ignored PET imaging. There is now evidence for 18fluorocholine PET in localising parathyroid adenomas not visualised by those two modalities and this therefore allows a targeted surgical approach to be performed in a higher number of patients. This technique is being used by some centres routinely already prior to a first operation due to its ability to detect adenomas in the vast majority of patients not identified by US and sestamibi. I appreciate that not all centres have this availability but thought it should at least be included in the guidelines as an important option if available."	Thank you for your comment. We did not identify any evidence for PET scanning. PET is an emerging imaging modality and is not widely available and it is very expensive. We are aware of the potential role of PET scanning in the management of failed initial neck exploration and persistent disease. We have flagged this to the NICE surveillance team as this may be an area for future update. The recommendations are permissive around the second imaging modality, in line with the evidence reviewed. We have been prescriptive about one ionising radiation test for safety reasons.

**None of the stakeholders who commented on this clinical guideline have declared any links to the tobacco industry.*

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