National Institute for Health and Clinical Excellence

Name of guideline Familial Breast Cancer update
Guideline Consultation Comments Table
Tuesday 15th January 2013 – Monday 25th February 2013

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	Association of Breast Surgery	1	NICE	30		1.6.3 (Sorry no line numbers on this document) – Is there an upper age limit for high risk > 40 years to be offered annual mammography? Perhaps aged 69 as in 1.6.13?	Thank you for your comment. The GDG have revised the recommendations to clarify the age ranges where surveillance should be available for all the moderate and high risk groups. The GDG have acknowledged in the guideline that there was no evidence specifically relating to surveillance for women aged 70 years and over and could therefore make no specific, evidence-based recommendations. However, the GDG agreed that as these women remained at risk of breast cancer, they should still have access to surveillance. In the absence of any evidence to support enhanced surveillance, the GDG agreed that the best course of action was to recommend that these women should remain in or return to the standard population screening programme.
SH	Association of Breast Surgery	2	Full NICE	116-117 31		1.6.8 – This recommendation is very vague and no use to clinicians – it should either be recommended or a research topic	Thank you for your comment. The GDG decided to recommend "consider annual mammographic surveillance for women aged 50 years and over at moderate risk of

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							breast cancer" as the evidence base for benefit in this population was not strong. 'Offer' is appropriate wording for a recommendation where the GDG is confident that, for the vast majority of people, the recommendation will do more good than harm. 'Consider' is the appropriate wording for a recommendation where the benefit is less certain and where a discussion about risks and benefits is required. Inevitably this may result in inconsistencies of practice that will reflect patient choice.
SH	Association of Breast Surgery	3	Full NICE	116-117 31		1.6.11 – The NHS BSP guidance for women at very high risk eligible for MRI scanning includes a comment that MRI scanning can be considered > 50 years where there is a dense background pattern. Could the guidelines be consistent to avoid confusion?	Thank you for your comment. We agree and have amended these recommendations to say 'do not offer MRI, unless mammography has shown a dense breast pattern'.
SH	Association of Breast Surgery	4	NICE			Generally the guidelines are very clear and it is good that their scope includes women at high familial risk with previous history of breast cancer	Thank you.
SH	Association of Genetic Nurses and Counsellors (AGNC)		Full	23	2	We feel that this algorithm does not take account women affected at a young age but do not have a family history, who are essentially at moderate risk and should therefore be managed in secondary care e.g. A woman with breast cancer aged 35 and no FH.	Thank you. We believe that the recommendations in the guideline and the accompanying algorithms account for young women without a family history. We have now simplified the algorithms and removed any duplication. We have presented separate pathways within each algorithm for people

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							with and without a personal history of breast cancer. The algorithm has also been updated to reflect any changes made to the recommendations, and in response to comments received from stakeholders.
SH	Association of Genetic Nurses and Counsellors (AGNC)	1	Full	20	13	We agree that it is beneficial to inform stakeholders, confidentially, of the content of the guidelines in advance of their release as this enables them to prepare for patient/public enquiries and for implementation. However, we are disappointed that similar consideration was not given to release of the draft guidelines. Stakeholders received no advance communication regarding release date or content of guidelines giving no time to prepare for the influx of patient enquiries the draft guideline initiated. This was exacerbated by widespread media coverage, which was the first communication many stakeholders heard about the release of the draft recommendations. This leaves services, and consequently patients, vulnerable to misinformation and associated anxiety. This element of the process could be greatly improved.	Thank you for your comment. We have discussed your concerns with NICE about the timing of the press release and the amount of notice that was given. They are now considering ways to improve this process for future guidelines.
SH	Association of Genetic Nurses and Counsellors (AGNC)	2	Full	22	4	We would suggest that the box specifying "Known cancer-predisposing gene change in family, e.g. BRCA1, BRCA2, TP53" be more appropriate before the box above "At least: - One 1st degree relative with breast cancer before 40 - Two 1st degree relatives or one 1st degree and one 2nd degree relative with breast cancer at any age". We are concerned that without this change some individuals at increased risk may be missed by primary care.	Thank you for your comment. We agree and have moved the box specifying 'Known cancer-predisposing gene change in family, e.g. BRCA1, BRCA2, TP53' to be the first decision within the algorithm.
SH	Association of Genetic Nurses and Counsellors (AGNC)	3	Full	23	2	We would suggest that the box specifying "Known cancer-predisposing gene change in family, e.g. BRCA1, BRCA2, TP53" be more appropriate before	Thank you for your comment. We agree and have moved the box specifying 'Known cancer-

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						the box above "Diagnosis before age 60?". We are concerned that some individuals may not recognise the importance of BRCA or other high risk gene changes irrespective of age of diagnosis.	predisposing gene change in family, e.g. BRCA1, BRCA2, TP53' to be the first decision within the algorithm.
SH	Association of Genetic Nurses and Counsellors (AGNC)	4	Full	24	2	Following the box in the bottom right stating "10 year risk less than 3% at age 40? " we think there is a typographical area. Yes and no are the wrong way round. Women at less than 3% risk should be managed in primary care and those greater than 3% risk should be managed in secondary care.	Thank you for your comment. We have now simplified this part of the algorithm to say 'Assess the level of risk'.
SH	Association of Genetic Nurses and Counsellors (AGNC)	5	Full	27	45	The majority of patients attending a cancer genetics clinic are seen by a genetic counsellor rather than a consultant cancer geneticist. We are concerned that the views of this key professional group were not sought or included in the methodology web-based surveys.	This is a valid point and could be considered when the guidelines are next updated. The aim of the questionnaire was to ask clinicians how they manage patients with familial breast cancer in their respective centres. In the majority of cases, we would expect that cancer geneticists and genetic counsellors at any centre would manage patients based on the local/national guidelines agreed in their specific centre.
SH	Association of Genetic Nurses and Counsellors (AGNC)	6	Full	30	14	Clarification of which Manchester Scoring System has been considered throughout the guideline, and which should be employed, would be helpful. Does this relate to the original scoring system or that including adjustments for pathology.	The questionnaire asked about various risk assessment tools including Manchester score, with the aim of comparing the utility of various risk assessment tools in different centres. We have removed reference to the Manchester scoring systems from recommendations other than those in Chapter 2.
SH	Association of Genetic	7	Full	38	12	Has there been consideration in light of new	Thank you for your comment.

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	Nurses and Counsellors (AGNC)					recommendations for use of chemoprevention, about whether verification of breast cancer diagnoses should be undertaken where clinically relevant, particularly in distant relatives where reported diagnoses are less reliable? This may be relevant for mod risk individuals managed solely in 2nd care.	Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	Association of Genetic Nurses and Counsellors (AGNC)	8	Full	42	8	Please add to recommendation that it is not expected that individuals in secondary care should use BOADICIEA or other carrier prediction calculators.	Thank you for your comment. We do not consider that the recommendation for using carrier probability calculation in secondary care indicates an expectation that this should be done, only that it is recommended and available to appropriately trained healthcare professionals.
SH	Association of Genetic Nurses and Counsellors (AGNC)	9	Full	43	30	Applaud and fully support the recommendation for further research into developing and validating new models for calculating carrier probability which take into account additional relevant factors.	Thank you.
SH	Association of Genetic Nurses and Counsellors (AGNC)	10	Full	43	41	Numerical risk can sometimes cause more problems for individuals as this gives unrealistic assumptions about accuracy of the calculation. Important to emphasise the importance of how risk is framed.	Thank you for your comment. Geneticists are trained to communicate risk and frame the risks and benefits in ways which are understood by each individual. This is also addressed in the guideline (see recommendations on page 62).
SH	Association of Genetic Nurses and Counsellors (AGNC)	11	Full	50	2	From a practical perspective who will be responsible for preparing information about genetic testing and the risk and benefits of risk reducing surgery. There will be challenges in agreeing a national consensus and retaining local accuracy.	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.

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SH	Association of Genetic Nurses and Counsellors (AGNC)	12	Full	63	14	Do the two sessions of genetic counselling refer to pre-test counselling?	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	Association of Genetic Nurses and Counsellors (AGNC)	13	Full	64	9	The AGNC committee feel that genetic counselling practice across the country has changed. In many centres it is no longer a necessity to do two pre-test genetic counselling appointments for most predictive or diagnostic testing for a family history of breast cancer. Regional genetics centres are not prescriptive about this and tailor counselling to the individual patient and circumstances. There have been a number of conference and other publications regarding deviation from the traditional predictive test model for family histories of breast cancer which should be considered e.g. Taylor et al., BSHG 2011).	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	Association of Genetic Nurses and Counsellors (AGNC)	14	Full	64	9	We feel that these recommendations need to be more specific about what constitutes appropriate training for healthcare professionals undertaking genetic testing discussions. Without such consideration, patients are vulnerable to inconsistency in standards of genetic counselling.	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	Association of Genetic Nurses and Counsellors (AGNC)	15	Full	70-83		Do the economic calculations assume a reduction in screening if an unaffected individual receives a negative BRCA gene screen? Is screening expected to be reduced in unaffected individuals with a negative BRCA screen? If so, how should this be calculated / managed?	Thank you for your comment. In order to derive costs for individuals in the healthy state, the GDG specified different screening strategies according to BRCA status. Women known to be BRCA positive were assumed to receive MRI screening, while those known

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							to be BRCA negative received no screening. Women with unknown BRCA status received screening dependent on their carrier probability; with mammography used at less than 30% carrier probability and MRI at 30% or more.
SH	Association of Genetic Nurses and Counsellors (AGNC)	16	Full	85	10	We welcome the reduction in threshold for offering genetic testing for alterations in BRCA1 and BRCA2 to affected individuals. However, we have concerns about the huge increase in workload for genetic counselling services and laboratory services this will cause and how this will be funded, particularly as cost benefits of reduced screening impact upon secondary care budgets rather than those in tertiary care.	Thank you for your comment. The recommendations to consider genetic testing at 5-10% have been removed from the guideline. The GDG agreed that lowering the threshold to 5% would increase the number of patients eligible for genetic testing and potentially overload the existing service. In addition the GDG did not wish to recommend a lower threshold than most other countries worldwide who offer genetic testing.
SH	Association of Genetic Nurses and Counsellors (AGNC)	17	Full	85	10	Our membership have raised concerns that the decrease in threshold, as well as the recommendation that testing in unaffected individuals should be considered, will create a huge increase in workload for already stretched genetic counselling and laboratory services. There are also concerns on how this will be funded.	Thank you for your comment. The recommendations to consider genetic testing at 5-10% have been removed from the guideline. The GDG agreed that lowering the threshold to 5% would increase the number of patients eligible for genetic testing and potentially overload the existing service. In addition the GDG did not wish to recommend a lower threshold than most other countries worldwide who offer genetic testing.
SH	Association of Genetic Nurses and Counsellors	18	Full	85	10	Use of the word "consider" in a publicly available document may lead to inconsistency of practice and	Thank you for your comment. 'Offer' is appropriate wording for a

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	(AGNC)					unfairly raise patient expectations of what genetic services can offer.	recommendation where the GDG is confident that, for the vast majority of people, the recommendation will do more good than harm. 'Consider' is the appropriate wording for a recommendation where the benefit is less certain and where a discussion about risks and benefits is required. Inevitably this may result in inconsistencies of practice that will reflect patient choice.
SH	Association of Genetic Nurses and Counsellors (AGNC)	19	Full	85	10	The Manchester scores presented appear confusing in the 3rd and 4th bullet points with a 20% threshold appearing to be equivalent to a Manchester score of 17 and a Manchester score of 16.	Thank you for your comment. We have removed reference to the Manchester Score from the guideline as it is one of several methods of providing an estimate of probability of finding a mutation, and therefore no does warrant being given special attention. The model was based on a percentage threshold which we have retained for consistency
SH	Association of Genetic Nurses and Counsellors (AGNC)	20	Full	85	10	We welcome the recommendation that variants of uncertain significance be reviewed regularly. However, it is not clear how laboratories should be doing this. We also feel it should be clarified that any change in the pathogenicity of a variant should be fed back to the genetic counselling service who requested the test. It is the responsibility of laboratories to feed back to referrers and they in turn should contact families as appropriate.	Thank you for your comment. We have amended and expanded this recommendation to include advice on the potential risk and benefits of genetic testing and inform families with no clear genetic diagnosis that they can request review in the specialist genetic clinic at a future date. You have also raised some issues

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							relating to service guidance which we were not included in this topic and therefore we are unable to make recommendations. However they are an implementation issue and will be highlighted to the Implementation Team at NICE
SH	Association of Genetic Nurses and Counsellors (AGNC)	21	Full	91	7	The use of the words "do not" seem too prescriptive	We disagree. There was no evidence that a delay in genetic testing at diagnosis of breast cancer affected overall survival so the GDG were not able to recommend rapid genetic testing. Therefore, we have amended the recommendations to say 'Offer fast track genetic testing (within 4 weeks of a diagnosis of breast cancer) only as part of a clinical trial.'
SH	Association of Genetic Nurses and Counsellors (AGNC)	22	Full	91	7	The problem with offering rapid testing only through a clinical research trial is that there is a lack of such trials nationally.	Thank you for your comment. We have made a research recommendation to determine the benefits and harms of creating a rapid access genetic testing service for people with a new diagnosis of breast cancer. A NICE research recommendation can improve the chances of trials being funded.
SH	Association of Genetic Nurses and Counsellors (AGNC)	23	Full	95	6	What is considered appropriate and up to date training for healthcare professionals offering such consultations? Who is offering this training to these individuals?	Thank you for your comment. We have amended this recommendation to 'offer a detailed consultation with a clinical geneticist or genetics counsellor'.
SH	Association of Genetic Nurses and Counsellors	24	Full	96	2	We welcome the recommendation for additional research into the best way of offering fast track	Thank you.

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	(AGNC)					testing and the medical, psychological and social benefits and risks to the patient and their family.	
SH	Association of Genetic Nurses and Counsellors (AGNC)	25	Full	116	1	Bullet point 2 regarding offering annual mammographic surveillance to all women age 40 and over at high risk. Please clarify that this includes BRCA1 and BRCA2 carriers. Please specify that TP53 carriers are not included in this recommendation.	Thank you for your comment. We have amended these recommendations and further clarified the specific level of surveillance for each of the six groups. TP53 carriers are now included.
SH	Association of Genetic Nurses and Counsellors (AGNC)	26	Full	116	1	We are not clear on the evidence base for the consideration of offering annual mammographic surveillance to women at moderate risk over the age of 50 or how this should be delivered.	Thank you for your comment. This is addressed by the following explanation in the LETR paragraph (page 139) 'Most of the studies were in people at high risk of breast cancer so the effectiveness of surveillance in those at moderate risk had to be extrapolated from this evidence.' This lack of evidence meant the GDG made a 'consider' rather than 'offer' recommendation.
SH	Association of Genetic Nurses and Counsellors (AGNC)	27	Full	116	1	Bullet point 9 - Typographical error *BCRA* should be written as *BRCA.*	Thank you for your comment. Thank you we have made this amendment.
SH	Association of Genetic Nurses and Counsellors (AGNC)	28	Full	116	1	Please clarify the evidence for offering women who are TP53 carriers mammographic surveillance as part of the national screening programme after the age of 50, particularly concerning radiation risks in this group of individuals.	Thank you for your comment. We have made this particular issue for TP53 carriers clearer in the LETR paragraph.
SH	Association of Genetic Nurses and Counsellors (AGNC)	29	Full	116	1	We welcome the recommendation that women who have on-going concerns should be offered additional psychological support. However, we highlight that there is a lack of appropriate psychological support services nationally.	Thank you for your comment. We hope that these recommendations will enhance the provision of what we believe to be a valuable service.
SH	Association of Genetic	30	Full	116	1	We are concerned that women who are at 50% risk	Thank you for your comment. We

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	Nurses and Counsellors (AGNC)					of inheriting a BRCA2 mutation will not be offered MRI surveillance from 30-49. We appreciate that there is evidence to show that BRCA2 related breast tumours have a tendency to develop later and may be more easily picked up using mammography than tumours associated with BRCA1. However, our members have highlighted a large number of families with confirmed BRCA2 mutations, where there is consistent young onset of breast cancer under the age of 40. We are extremely concerned that women at 50% risk of carrying a BRCA2 mutation may feel pressured and coerced into having predictive genetic testing before they are psychologically ready for that result, as this will be the only way that they can access MRI breast surveillance.	have amended the recommendation to 'Offer annual MRI surveillance to women: • aged 30-49 years with a greater than 30% probability of being a BRCA carrier • aged 30-49 years with a known BRCA1 or BRCA2 mutation.
SH	Association of Genetic Nurses and Counsellors (AGNC)	31	Full	137	18	We are not clear why BRCA gene carriers with a personal history of breast cancer have annual surveillance up the age of 69, but in those women at moderate and high risk, or unaffected gene carriers have screening indefinitely.	Thank you for your comment. We have amended these recommendations for consistency
SH	Association of Genetic Nurses and Counsellors (AGNC)	32	Full	137	18	What is definition of high contralateral risk?	Thank you for your comment. We have deleted the word 'contralateral' from these recommendations to avoid confusion.
SH	Association of Genetic Nurses and Counsellors (AGNC)	33	Full	100-142		Welcome more specific guidance on what screening should be offered to women at an increased lifetime risk of developing breast cancer. However, we feel that within the draft document there appear to be inconsistencies in these recommendations.	Thank you for your comment. These recommendations have been revised.
SH	Association of Genetic Nurses and Counsellors (AGNC)	34a	Full	164	6	We have a number of questions and concerns regarding the recommendations on the use of tamoxifen and raloxifene in women with no personal history of breast cancer. In practical terms:	Thank you for your comments.

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						- Who is going to prescribe these drugs to these women in practice?	The GDG agreed that the oncologist would first prescribe tamoxifen but the GP would take over this responsibility.
						- How will these drug regimens be funded?	This is an issue for implementation and will be highlighted to the Implementation Team at NICE.
						- Given that there is a significant risk of side effects for these drugs, which health professionals will be responsible for monitoring these women while they are taking these drugs?	The prescriber would be responsible for monitoring these women.
						- At what age is it recommended that women commence this regimen?	Thank you for your comment. The GDG agreed not to set a minimum age limit for accessing tamoxifen or raloxifene, as they did not want to prevent young women from having access to preventative treatment as there may be some who wish to discuss options other than risk reducing surgery.
SH	Association of Genetic Nurses and Counsellors (AGNC)	34b	Full	164		We are concerned regarding the fact that neither drug is currently licenced for this use in the European Union.	Thank you for your comment. This fact is taken into consideration when evaluating the evidence. The MHRA were invited to respond and they raised no concerns.
SH	Association of Genetic Nurses and Counsellors (AGNC)	35	Full	164	6	We would welcome more guidance on the practicalities of dealing with other hormonal issues such as the use of contraception in these women. Although we recognise that the rate of pregnancy conception in women taking tamoxifen is likely to be	Thank you for your comment. This is covered within the recommendation on discussing side effects of chemoprevention and stopping tamoxifen if

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						low, we would welcome guidance on the management of this eventuality.	considering conceiving.
SH	Association of Genetic Nurses and Counsellors (AGNC)	36	Full	164	6	Many women with BRCA1 mutations are at an increased risk of triple negative breast tumours. Is the use of tamoxifen or raloxifene in these women likely to be of any benefit given their tumour pathology risks?	Thank you for your comment. There was insufficient evidence of a specifically different effect in BRCA gene carriers. So we have amended the background section to include the ER specific risk reduction. Therefore the recommendations have not been amended as the risks should be discussed on an individual basis.
SH	Association of Genetic Nurses and Counsellors (AGNC)	38	Full	164	6	Has any thought been given to the risks associated with use of these drugs in women with a family history, but no personal history, of endometrial cancer?	Thank you for your comment. This is a factor that would influence a women's choice, but there was no evidence to allow us to make a specific recommended.
SH	Association of Genetic Nurses and Counsellors (AGNC)	39	Full	164	6	When considering the use of tamoxifen in pre-menopausal women at moderate risk, the recommendations do not specify that this should not be offered in women with a personal history of endometrial cancer or thromboembolic disease.	Thank you for your comment. However, you are incorrect. The recommendation specifically excludes women with a history of thromboembolic disease or endometrial cancer.
SH	Association of Genetic Nurses and Counsellors (AGNC)	40	Full	168	23	There is no risk threshold stated at which it would be appropriate to offer risk reducing bilateral mastectomy or risk reducing bilateral salphingo oophorectomy.	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	Association of Genetic Nurses and Counsellors (AGNC)	41	Full	180	8	In light of the significant risk of occult cancers in gene carriers and women at high risk, should there be guidance on how surgical specimens from risk reducing breast and ovarian surgeries are evaluated histologically?	Thank you for your comment. This is clearly an important issue. However, it did not form part of the scope of the guideline. We recommend you contact the Royal College of Pathologists to discuss

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							this further.
SH	Association of Genetic Nurses and Counsellors (AGNC)	42	Full	General		Lack of consistency between NICE guidelines and current National Screening Committee guidelines may affect implementation	Thank you for your comment. The guideline was produced based upon the best available clinical and cost effectiveness evidence. Thank you for your comment. The GDG, NCC-C and NICE will be working closely with the NHSBSP to consider whether national screening protocols for higher risk women should be updated to reflect the updated NICE guideline. This is also an issue for implementation of the guideline and will be highlighted to the Implementation Team at NICE.
SH	Birmingham Women's Hospital	1	Full	20	13	It would have been helpful for Stakeholders to have advance notice of release of the draft guidelines, particularly given the wide media interest and coverage of the chemoprevention recommendations. It was difficult to field enquiries from patients and the public without prior notification.	Thank you for your comment. We have discussed your concerns with NICE about the timing of the press release and the amount of notice that was given. They are now considering ways to improve this process for future guidelines.
SH	Birmingham Women's Hospital	2	Full	22	4	We believe the question about the presence of known cancer predisposing gene mutations (BRCA1, 2 or TP53) should be asked before questions about family history to ensure individuals from this family are referred appropriately. This is particularly important where there is little or no family history in relatives who are related through the paternal line.	Thank you for your comment. We agree and have moved the box specifying 'Known cancer-predisposing gene change in family, e.g. BRCA1, BRCA2, TP53' to be the first decision within the algorithm.
SH	Birmingham Women's Hospital	3	Full	23	2	Again, we believe the question about presence of known cancer predisposing gene mutations should	Thank you for your comment. We agree and have moved the box

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						appear before that on age of diagnosis as this criteria supersedes any age criteria. We also believe the box 'Are any of these additional factors present?' should include a paternal family history of ovarian cancer and possibly also a paternal family history of prostate cancer <50 or in >1 relative.	specifying 'Known cancer-predisposing gene change in family, e.g. BRCA1, BRCA2, TP53' to be the first decision within the algorithm. These recommendations were not updated during development of the guideline and so we are unable to make any changes to this box.
SH	Birmingham Women's Hospital	4	Full	24	2	The box '10yr risk less than 3% at age 40' should read '10yr risk greater than 3% at age 40'.	Thank you for your comment. We have now simplified this part of the algorithm to say 'Assess the level of risk'.
SH	Birmingham Women's Hospital	5	Full	general		Reference to the demand for family history collection tools for use in primary and secondary care to facilitate subsequent transfer of information would be useful.	Thank you for your comment. This is an implementation issue and we will forward your comments to the implementation team at NICE.
SH	Birmingham Women's Hospital	6	Full	36	Table 2.1	These three measures of risk category may not be equivalent for an individual. Which should take priority? In practice, the lifetime risk for most individuals would not be calculated from 20, but from the age at presentation to clinical genetics.	Thank you for your comment. We agree that they would not be equivalent and we have not stated that they are. They are definitions which help to determine the appropriate surveillance protocol or eligibility for genetic testing. We acknowledge that this is a complicated area.
SH	Birmingham Women's Hospital	7	Full	43	41	Discussion of numerical risk with individuals can be unhelpful. May imply an unrealistic degree of accuracy in calculation of risk. We feel it is more important for patients to have an appreciation of how their risk relates to that of the general population and how this influences surveillance	Thank you for your comment. Geneticists are trained to communicate risk and frame the risks and benefits in ways which are understood by each individual. This is also addressed in the

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						recommendations etc. In our experience, individuals can become overly anxious about their percentage risk.	guideline (see recommendations on page 62).
SH	Birmingham Women's Hospital	8	Full	50	2	There will be a need for national standard information leaflets to be developed to fulfil these guidelines on provision of information. It is unclear who will develop these and how this will be achieved.	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	Birmingham Women's Hospital	9	Full	64	9	Many centres now carry out presymptomatic testing in one session if appropriate (on a case by case basis). More important that there should be provision for adequate time across an appropriate number of sessions for provision of information, pre-test counselling and discussion of patients concerns and needs.	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	Birmingham Women's Hospital	10	Full	64	9	'Discussion of genetic testing should be undertaken by a healthcare professional with appropriate training' is vague. We believe there should be greater specification of what constitutes appropriate training. We believe that this should specify that testing should be carried out by a professional who is part of a clinical genetics service.	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	Birmingham Women's Hospital	11	Full	85	10	As the cost of genetic testing is decreasing, we believe these guidelines would be more future proof if they also clearly indicated the cost per mutation identified at which testing is effective. This would allow those organising genetics services to adapt their testing criteria as the cost of testing decreases.	Thank you for your comment. The cost of genetic tests has been included within the model and we do not believe it is appropriate to include costs within recommendations.
SH	Birmingham Women's Hospital	12	Full	85	10	We applaud the reduction in the threshold for testing affected individuals as we believe this will greatly benefit patients and families. However, we are concerned about the impact of this on workload and budgets of clinical and laboratory genetic services. Given that the benefits are realised	Thank you for your comment. However in response to the concerns you have raised and those from other stakeholders the recommendations to consider genetic testing at 5-10% have now

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						outside of genetics, we feel it should be highlighted that this will require increased funding for these services.	been removed from the guideline. The GDG agreed that lowering the threshold to 5% would increase the number of patients eligible for genetic testing and potentially overload the existing service. In addition the GDG did not wish to recommend a lower threshold than most other countries worldwide who offer genetic testing.
SH	Birmingham Women's Hospital	13	Full	85	10	There is no mention of genetic testing for other genes in this section. Given the increase in panel tests due to next generation sequencing, it would be helpful for the utility of testing for other genes with known associations with breast cancer to have been considered e.g. PTEN, CHK2, RAD51c etc. Is there a minimum gene set that should be tested? Should laboratories be testing TP53 (and/or other genes) together with BRCA1 and BRCA2.	Thank you for your comment. These mutations are very rare and therefore were not prioritised for inclusion in this guideline.
SH	Birmingham Women's Hospital	14	Full	85	10	A recommendation for testing for individuals with no personal history of breast cancer, where an affected family member is unavailable, is useful and likely to bring benefit for patients. However, for this to be cost effective, the surveillance for these individuals would need to be reduced if a mutation was not identified. It is not clear from the guidelines, how this modified risk should be calculated or how this screening should be amended. In addition, there is no mention of the benefit of testing multiple unaffected family members, the additional information this provides and how this should be interpreted.	Thank you for your comment. We have amended the recommendations, but it impossible to make a specific recommendation for a situation that varies for each individual.
SH	Birmingham Women's	15	Full	85	10	Greater clarity on the frequency and methodology	Thank you for your comment. We

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	Hospital					for reviewing VUS. A formalised review process following current best practise guidelines for the assessment of rare and novel genetic variants (CMGS, 2013) would demand significant resource. Clarity that this information should be relayed to referrers to re-contact the patient would be helpful.	have amended these recommendations and included appropriate sub-headings for simplicity.
SH	Birmingham Women's Hospital	16	Full	85	10	The reduction in threshold for testing to 10% (and consider and 5%) may result in some individuals managed in secondary care meeting criteria for genetic testing. This could create inconsistencies in access to genetic testing depending on local pathways.	The recommendations to consider genetic testing at 5-10% have been removed from the guideline. The GDG agreed that lowering the threshold to 5% would increase the number of patients eligible for genetic testing and potentially overload the existing service. In addition the GDG did not wish to recommend a lower threshold than most other countries worldwide who offer genetic testing.
SH	Birmingham Women's Hospital	17	Full	92	30	We welcome the recommendations for further research on the pathways, risks and benefits of rapid genetic testing.	Thank you.
SH	Birmingham Women's Hospital	18	Full	116-117	1	The increase in screening to annual mammograms from 40 for women at moderate and high risk will more than double the screening required from screening units. Can this realistically be delivered?	Thank you for your comment. This recommendation remains unchanged from the 2004 guideline, and there was no new evidence to support a change.
SH	Birmingham Women's Hospital	19	Full	116-117	1	While individuals at 30% risk of BRCA1 are eligible for early MRI screening, those at risk of BRCA2 are not. In our experience some BRCA2 families exhibit a family history consistent with a very high risk and young age of onset (similar to BRCA1). In such families, those at 50% risk would not be eligible for MRI at all or for Mammography below age 40. This may coerce individuals to have genetic testing when they are not psychologically ready.	Thank you for your comment. This recommendation remains unchanged from the 2006 guideline, and there was no new evidence to support a change. We agree there is a degree of risk but believe it will only apply to a small number of women as most

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							would pursue testing.
SH	Birmingham Women's Hospital	20	Full	137	18	It would be helpful to clarify ' a high risk of contralateral breast cancer' and to suggest validated tools to calculate this. There is inconsistency in offering women with a personal history of breast cancer, and a BRCA mutation, mammography from 50-69 when the national screening programme is being extended until 73. Also, women with a BRCA mutation but no personal history have no upper age limit for mammography (p.116-117) while those with a personal history cease at age 69. Equally, women with a personal history and a BRCA mutation are not eligible for mammograms age 30-49 alongside MRI scans, whereas those without a personal history receive both. This does not appear logical or equitable	Thank you for your comment. We have amended these recommendations for clarity. We have also deleted the word 'contralateral' from these recommendations to avoid confusion. No validated tools are available to measure a person's risk if they have had breast cancer. Thank you for your comment. We have amended these recommendations for consistency which now include the following; 'Offer mammography as part of the population screening programme for all women aged 70 years and over with a personal history of breast cancer who: - remain at high risk of breast cancer (including those who have a BRCA1 or BRCA2 mutation, and - do not have a TP53 mutation'.
SH	Birmingham Women's Hospital	21	Full	general		If women are taking Tamoxifen or Raloxifine to reduce their risk, should their risk and surveillance be adjusted accordingly? If so, how should this be calculated?	Thank you for your comment. Although chemoprevention is attempting to reduce risk it impossible to measure any reduction of risk on an individual basis. We have clarified in the LETR paragraph on page 186 of the guideline the reasons for this.
SH	Birmingham Women's	22	Full	164	6	Is it appropriate for healthcare professionals in	Thank you for your comment. This

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	Hospital					genetics to provide information on the risks of chemoprevention when they are unlikely to prescribe the medication, or to monitor patients response, side effects etc. Will standard information be developed for national use? Who will prescribe chemoprevention, follow up and monitor these patients.	is an issue for implementation and will be highlighted to the Implementation Team at NICE.
SH	Birmingham Women's Hospital	23	Full	164	6	If patients have had BSO and are taking HRT, how would this influence advice regarding tamoxifen use.	Thank you for your comment. Women taking HRT after oophorectomy would not be offered an anti-oestrogen they would be advised to stop the HRT.
SH	Birmingham Women's Hospital	24	Full	164	6	'Consider' use of chemoprevention in moderate risk women. Clarity over the criteria for when this would be appropriate would be helpful.	Thank you for your comment. 'Offer' is appropriate wording for a recommendation where the GDG is confident that, for the vast majority of people, the recommendation will do more good than harm. 'Consider' is the appropriate wording for a recommendation where the benefit is less certain and where a discussion about risks and benefits is required. Inevitably this may result in inconsistencies of practice that will reflect patient choice. A definition for offer and consider has been added to the methodology section of the full guideline.
SH	Birmingham Women's Hospital	25	Full	168	23	It would be helpful to have some reference to the risk at which RRM is appropriate as this would facilitate consistency of access for women and clarity for clinicians. E.g. RRM should be	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation

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						offered/discussed with women at high risk and may be considered by those at ? moderate risk/? >25% risk.	process. As these refer to sections that were not updated we are unable to comment.
SH	Birmingham Women's Hospital	26	Full	180	8	Clearly quantifying the risk of cancer in the other breast is difficult. Are there any recommended validated tools. The estimate of this may also vary across the multidisciplinary team leading to inconsistency for patients.	Thank you for your comment. No - there are not any validated tools, but there is literature looking at empirical estimates. We acknowledge that it is difficult to assess the contralateral breast cancer risk and specialists will need to refer to the relevant literature for empirical estimates.
SH	Birmingham Women's Hospital	27	Full	General		Overall, we congratulate the GDG, NCC and NICE on the successful production of this very detailed and widely evidenced guideline. We believe changes to the surveillance, genetic testing and risk reduction recommendations will be of great benefit to patients with a personal and family history of cancer and their families. The new guidance addressing surveillance for those with a personal and family history of breast cancer will be particularly beneficial in reducing inconsistency for this group. We applaud the call for greater research on the pathways and patient implications of rapid genetic testing. After extensive consideration we have commented on several areas. We appreciate some aspects of these relate to implementation challenges. However, in some cases it would be helpful to highlight these potential difficulties to facilitate future commissioning discussions.	Thank you. Thank you, we agree. Thank you, this issue will be highlighted to the Implementation Team at NICE
SH	Breakthrough Breast	1	Full	Gener		This submission reflects the views of Breakthrough	Thank you for your comments.

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	Cancer			al		Breast Cancer, based on our experience of working with people with a family history of breast cancer or a professional or personal interest in this area. In particular our submission to this consultation reflects the results of two surveys carried out by Breakthrough in August 2012 (43 responses) and February 2013 (61 responses) where respondents were asked to comment on the state of family history services, improvements needed and (in the February 2013 survey only) specific aspects of the draft Familial Breast Cancer guidelines. Quotes in italics below are taken from free text responses to these surveys.	
SH	Breakthrough Breast Cancer	2	Full	General		Largely, people with, or with an interest in, a family history of breast cancer replying to Breakthrough's February 2013 survey felt positively about the recommendations laid out in the draft guideline.	Thank you.
SH	Breakthrough Breast Cancer	3	General	General		Where text appears in both the Full and NICE versions of the guideline, Breakthrough has commented only on the Full guideline. Please assume that these comments apply equally to the corresponding text in the NICE version of the guideline.	Thank you for your comments.
SH	Breakthrough Breast Cancer	4	Full	5	3	These incidence statistics need to be updated to reflect the most recent data available. The latest statistics are that around 50,000 women and 400 men are diagnosed with breast cancer each year in the UK.* * Cancer Research UK. *Breast cancer statistics.* http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast [accessed 15 February 2013]	Thank you for your comment. This section has been updated with the latest CRUK statistics.
SH	Breakthrough Breast Cancer	5	Full	42 6	1	Breakthrough believes that the guideline on offering HRT after oophorectomy should be included as a key priority for implementation. ["When women with	Thank you for this information. We understand the concern raised by your members on this important

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				(KPI)		no personal history of breast cancer have either a BRCA1 or BRCA2 mutation or a family history of breast cancer and they have had a bilateral salpingo-oophorectomy before their natural menopause, offer them: • combined HRT if they have a uterus • oestrogen only HRT if they don't have a uterus until the time they would have expected natural menopause."] We have found that a significant number of women, having seen the draft guideline, are still deeply concerned about taking HRT after oophorectomy and, despite the guideline being the product of an expert panel and a review of the best scientific and clinical evidence, erroneously believe that taking HRT is extremely likely to lead to a breast cancer diagnosis even after oophorectomy. *"I can't see how taking a preventative measure such as surgery on the one hand and then prescribing a known risk factor medication in follow-up makes any sense whatsoever. This is one of those logics that should be tested on a Martian... clearly any Martian would say why bother with any preventative measure of any kind then?"* GPs are primarily responsible for prescribing HRT and it is vital they are made aware of the new guideline and the evidence behind it so that women have the opportunity to base their choice whether to take HRT on a rational and evidence-based assessment of possible benefits and risks. If this is not viewed as an implementation priority, it is likely that women will continue to either be denied HRT by their GP or decide not to take it based on a	issue, but the GDG are limited to 10 key priorities. The GDG used set criteria defined in the NICE guidelines manual (2012) to help them select their choices which are then voted upon. Unfortunately this topic was not selected.

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						misunderstanding of the relative likelihood of benefit versus risk. This would be concerning, as HRT could help relieve the potentially serious side effects of an early menopause in these women. *"[I am] worried that it will take GPs a long time to catch up on this as they have been told for so long not to prescribe HRT. [It] will be okay while you are with the GP who gets the consultant's advice but when you change GP or they retire/move on and you get a new one they rarely bother to read your notes and you end up having a row with them."*	
SH	Breakthrough Breast Cancer	6	Full	49 6 (KPI)	11	Breakthrough welcomes the inclusion of this recommendation as a key priority as people with a family history of breast cancer have repeatedly told us that there is a need for improved information and support in this area. In particular, we have been informed that there is insufficient information and support available in primary care as GPs are often unable to answer questions about family history. Therefore, when implementing this key priority attention must be given to raising awareness of the guideline at the primary care level and providing good information to GPs to enable them to support their patients.	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	Breakthrough Breast Cancer	7	Full	22	4	In the top box of the algorithm, the phrase "other issues raised about HRT and hormonal contraception" requires clarification. Does this mean that any woman approaching her GP and considering taking, stopping or changing HRT or hormonal contraception should have a first and second degree family history taken?	Thank you for your comment. We have deleted this phrase for simplicity and to avoid any misunderstanding.
SH	Breakthrough Breast Cancer	8	Full	23	2	The box reading "Known cancer-predisposing gene change in family, e.g. BRCA1, BRCA2, TP53" has no clear role in the algorithm.	Thank you for your comment. This box needs to be in the algorithm as it allows the GP direct referral

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							to the specialist genetics clinic if appropriate. We have moved the box specifying 'Known cancer-predisposing gene change in family, e.g. BRCA1, BRCA2, TP53' to be the first decision within the algorithm. We have now simplified the algorithms and removed any duplication. We have presented separate pathways within each algorithm for people with and without a personal history of breast cancer. The algorithm has also been updated to reflect any changes made to the recommendations, and in response to comments received from stakeholders.
SH	Breakthrough Breast Cancer	9	Full	23	2	The large boxes to left and right should be labelled "Do they meet *any of* the following criteria" to clarify that the person does not have to meet all criteria in the box to qualify for referral.	Thank you for your comment. We have amended both of these boxes, and have simplified the whole algorithm and removed any duplication. We have presented separate pathways within each algorithm for people with and without a personal history of breast cancer. The algorithm has also been updated to reflect any changes made to the recommendations, and in response to comments received from stakeholders. As a result, the label to which you refer no longer exists.

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SH	Breakthrough Breast Cancer	10	Full	23	2	Breakthrough welcomes the inclusion of triple negative / medullary breast cancer before 50 as a criterion for referral to tertiary care, as we have heard from our supporters that it is currently difficult to get a referral for consideration of genetic testing when this is the only indication of high BRCA carrier probability. Recent research has indicated that people with a history of triple negative breast cancer under age 50 are likely to carry a fault in BRCA1.* * Robertson, L *et al* (2012). *BRCA1 testing should be offered to individuals with triple-negative breast cancer diagnosed below 50 years.* Br J Cancer Mar 13;106(6):1234-8.	Thank you for your comment. There was an error in the algorithm which we have now corrected. The recommendations that cover this topic clearly state a triple negative breast cancer under the age of 40 years¸ as there is no strong evidence for sporadic TNT at aged 40-49. Please see pages 73-76 of the full guideline.
SH	Breakthrough Breast Cancer	11	Full	24	2	In the box on the right labelled "check tertiary care referral criteria", it is unclear what the "tertiary care referral criteria" are. It can be assumed that this refers to the box on the left. This algorithm would be much clearer if this top right box were combined with the box on the left.	Thank you for your comment. This part of the algorithm has now been updated and replaced by a single box which summarises the referral criteria to a specialist genetics clinic. We have simplified each algorithm and removed any duplication. We have presented separate pathways within each algorithm for people with and without a personal history of breast cancer. The algorithm has also been updated to reflect any changes made to the recommendations, and in response to comments received from stakeholders.
SH	Breakthrough Breast Cancer	12	Full	24	2	Breakthrough believes that having triple negative / medullary breast cancer before 50 should be included as a criterion for referral to tertiary care to align with the algorithm on page 23. As we have	Thank you for your comment. The recommendations that cover this topic clearly state a triple negative breast cancer under the age of 40

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						stated above on line 10, it is important that people in this situation are considered for genetic testing.	years¸ as there is no strong evidence for sporadic TNT at aged 40-49. Please see pages 73-76 of the full guideline. We have included this recommendation in the algorithm as you suggest.
SH	Breakthrough Breast Cancer	13	Full	24	2	This algorithm does not provide information on considering chemoprevention for women at moderate risk. Most of these women will be managed in secondary, not tertiary care, and therefore reference should be made to the recommendations on chemoprevention for moderate risk women (found on page 164).	Thank you for your comment. The algorithm has been amended to reflect chemoprevention for moderate risk women.
SH	Breakthrough Breast Cancer	14	Full	25	1	Is a history of triple negative breast cancer before 50 usually included in models used to estimate carrier probability? If not, this should be specifically included as a criterion qualifying a person for genetic testing.* * Robertson, L *et al* (2012). *BRCA1 testing should be offered to individuals with triple-negative breast cancer diagnosed below 50 years.* Br J Cancer Mar 13;106(6):1234-8.	Thank you for your comment. The recommendations that cover this topic clearly state a triple negative breast cancer under the age of 40 years¸ as there is no strong evidence for sporadic TNT at aged 40-49. Please see pages 73-76 of the full guideline. We have also revised and simplified the 'Referral to a specialist genetic clinic' algorithm.
SH	Breakthrough Breast Cancer	15	Full	42	8	Is a history of triple negative breast cancer before 50 usually included in models used to estimate carrier probability? If not, this should be specifically included as a criterion qualifying a person for genetic testing.* * Robertson, L *et al* (2012). *BRCA1 testing should be offered to individuals with triple-negative breast cancer diagnosed below 50 years.* Br J Cancer Mar 13;106(6):1234-8.	Thank you for bringing this to our attention. This was an error which we have now corrected. The full set of recommendations that cover this topic clearly state 'a triple negative breast cancer under the age of 40 years'¸ as there is no strong evidence for sporadic TNT at aged 40-49. Please see pages 73-76 of the full guideline. Some calculation methods can

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							incorporate hormone receptor status and other pathology markers, for example, the Manchester score, BOADICEA and BRCAPRO.
SH	Breakthrough Breast Cancer	16	Full	50	2	This box should be updated to include information on new aspects of the updated Familial Breast Cancer guideline. For example, people in secondary and tertiary care will require information on chemoprevention options, and those considering risk-reducing surgery will require information on taking HRT after oophorectomy. People with a family history of breast cancer have repeatedly told Breakthrough that there is a need for improved information for people in their position. Therefore, it is vital that information is made readily available that covers all relevant aspects of care for people in primary, secondary and tertiary care.	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	Breakthrough Breast Cancer	17	Full	51	32	Breakthrough believes that having triple negative / medullary breast cancer before 50 should be included as a criterion for referral to tertiary care to align with the algorithm on page 23. As we have stated above on line 10, it is important that people in this situation are considered for genetic testing.	Thank you for bringing this to our attention. This was an error in the algorithm which we have now corrected. The full set of recommendations that cover this topic clearly state 'a triple negative breast cancer under the age of 40 years', as there is no strong evidence for sporadic TNT at aged 40-49. Please see pages 73-76 of the full guideline.
SH	Breakthrough Breast Cancer	18	Full	56	1	Breakthrough believes that having triple negative / medullary breast cancer before 50 should be included as a criterion for referral to tertiary care to align with the algorithm on page 23. As we have stated above on line 10, it is important that people in this situation are considered for genetic testing.	Thank you for bringing this to our attention. This was an error in the algorithm which we have now corrected. The full set of recommendations that cover this topic clearly state 'a triple negative

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							breast cancer under the age of 40 years', as there is no strong evidence for sporadic TNT at aged 40-49. Please see pages 73-76 of the full guideline.
SH	Breakthrough Breast Cancer	19	Full	58	1	"triple negative breast cancer under the age of 40 years" is included as a situation in which secondary care clinicians should seek further advice from a specialist genetics service. Breakthrough believes that this age limit should be raised to age 50, as there is evidence that triple negative cancers under this age are associated with a significant BRCA1 carrier probability.* * Robertson, L *et al* (2012). *BRCA1 testing should be offered to individuals with triple-negative breast cancer diagnosed below 50 years.* Br J Cancer Mar 13;106(6):1234-8.	Thank you for bringing this to our attention. This was an error in the algorithm which we have now corrected. The full set of recommendations that cover this topic clearly state 'a triple negative breast cancer under the age of 40 years', as there is no strong evidence for sporadic TNT at aged 40-49. Please see pages 73-76 of the full guideline.
SH	Breakthrough Breast Cancer	20	Full	85	10	In general, people with, or with an interest in a family history of breast cancer replying to Breakthrough's February 2013 survey welcomed the recommendations for increased access to genetic testing, in particular for those with no affected relative available to be tested. *"My mother died in 1996 and I had no living relatives diagnosed with cancer (plenty of dead ones....). If my mother hadn't had the foresight back then to request, on her deathbed, that a DNA sample be taken, I could not have been tested. Now sequencing a person's genetic code is so much simpler and cheaper it is madness to require that there be a living relative with cancer."* However, some people pointed out that this may mean relatives who have themselves declined	Thank you for your comment. We have amended this section to include a recommendation to discuss the implications of genetic testing.

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						genetic testing are made aware of their genetic status against their own wishes, as if their child tests positive it is extremely likely that they are positive for a BRCA fault as well. *"…if my mum didn't want to be tested but I did and I found out that I had got the gene I would then know that my mum had it."* Genetic counsellors should be expected to discuss this possibility with people considering testing and talk to them about how they might handle this possibility should it arise. Genetic counsellors may need additional training in how to deal with this situation.	The recommendations allow appropriately trained individuals to discuss all the implications of genetic testing including the scenario's you have highlighted.
SH	Breakthrough Breast Cancer	21	Full	85	10	Is a history of triple negative breast cancer before 50 usually included in models used to estimate carrier probability? If not, this should be specifically included as a criterion qualifying a person for genetic testing.* * Robertson, L *et al* (2012). *BRCA1 testing should be offered to individuals with triple-negative breast cancer diagnosed below 50 years.* Br J Cancer Mar 13;106(6):1234-8.	Thank you for your comment. The recommendations that cover this topic clearly state a triple negative breast cancer under the age of 40 years¸ as there is no strong evidence for sporadic TNT at aged 40-49. Please see pages 73-76 of the full guideline.
SH	Breakthrough Breast Cancer	22	Full	85	10	People with, or with an interest in, a family history of breast cancer have told Breakthrough that they do not understand what having a 10% (or 1 in 10) chance of having a fault in BRCA1 or BRCA2 means. Risk calculation will be carried out by a healthcare professional, but it is important that people concerned about their family history have an indicative way to tell whether or not they might be considered for genetic testing (for example, an general indication of how many family members would need to be affected by breast cancer at what	Thank you for your comment. We will pass them on to the Public Involvement Programme at NICE who will consider them for inclusion in the Information for the Public guidance (IFP). Some risk assessment tools are freely available on-line. A web hyper links for BOADICEA has been included in the guideline.

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						age in order to qualify). An indicative measure of this kind should be included in the patient version of the NICE guideline. *"[The recommendations] are positive on the whole but I have no idea what '.....need to have at least a 1 in 10 chance of having a fault...' means so it's somewhat confusing!"* *"How can a person know if there is a 1 in 10 chance of having a fault in one of the breast cancer genes unless that person is given the genetic test in the first place? This guideline sounds ambiguous."*	
SH	Breakthrough Breast Cancer	23	Full	116	1	In general, people with, or with an interest in a family history of breast cancer replying to Breakthrough's February 2013 survey welcomed the recommendations on surveillance for women with a family history but no personal history of breast cancer. *"This increased screening is a very positive move..."* *"It seems to reflect the fact that risk is not only due to BRCA1 and BRCA2 mutations, i.e. that you may be at significant risk but not have a known mutation. So, this group would hopefully have better access to more accurate screening."* *"Being empowered to be able to go for screening will give women the upper hand on this disease and earlier diagnosis saves lives so I welcome the proposed extension in screening services."*	Thank you for this information.
SH	Breakthrough Breast Cancer	24	Full	116	1	Some people with, or with an interest in, a family history of breast cancer have expressed concern	Thank you. We will pass on all this information to our colleagues in

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						that a women must reach a certain age to be eligible for annual mammography and MRI screening. The reasons for these age cut-offs need to be made very clear to those who are too young to qualify for enhanced surveillance. Therefore, Breakthrough would strongly support the addition of a recommendation on how to support this group of women by providing good information on why surveillance is not offered to their age group, how they might reduce their risk of breast cancer and how to be breast aware. The reasons for these age cut-offs should also be clearly explained in the patient version of the NICE guidance. *"I think that 40 is too old to start the screening."* *"I find it slightly concerning as a person with an increased risk that screening still seems to take place later in my life and not now."* *"I think that cancer will be missed because of*	the Patient Information Programme (PIP) at NICE to consider when developing the Information for the Public (IFP) document. The starting age for surveillance has been amended for these recommendations (see pages 135-138). However, in women under 30 years of age there is no evidence of effectiveness of mammography in detecting breast cancer and there continues to be a concern of the potential harm of radiation to young breast tissue and the incidence of radiation-induced cancers, see full guideline page 139- 140. Unfortunately these issues were not included as part of the evidence review for this topic therefore we unable to make any recommendations.

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						screening starting later."	
SH	Breakthrough Breast Cancer	25	Full	116	1	It is potentially very confusing that women at 30% BRCA1 carrier probability will be offered MRI surveillance whereas those at 30% BRCA2 carrier probability will not be. The reasons for this disparity should be made very clear in the patient guideline so that women are less likely to feel that they are being unfairly treated.	Thank you for your comment. This recommendation remains unchanged from the 2006 guideline, and there was no new evidence to support a change. The research has found evidence of greater benefit in BRCA1 than BRCA2 and this is summarised in the LETR statement. Thank you. We will pass this information to our colleagues in the Patient Information Programme department at NICE.
SH	Breakthrough Breast Cancer	26	Full	118	3	Breakthrough welcomes the simplicity of the programmes laid out in Table 7.5 as we believe this will facilitate implementation of the recommendations. However, we believe these could be simplified further by combining the "Group 3" and "Group 4" columns as the programmes described are identical for these two risk categories.	Thank you for your comment. For clarity we have now revised this table to include six distinct groups.
SH	Breakthrough Breast Cancer	27	Full	137	18	In general, people with, or with an interest in a family history of breast cancer replying to Breakthrough's February 2013 survey welcomed the recommendations on surveillance for women with a family history and personal history of breast cancer. In particular, they welcomed clarity on surveillance eligibility for this group as there were no previous guidelines applicable to them. *"If there were no guidelines before and there are some now that specifically recommend procedures then it can only be positive!"*	Thank you.
SH	Breakthrough Breast Cancer	28	Full	137	18	In these recommendations, the upper age limit for mammographic surveillance is 69 for women with a	Thank you for your comment. We have amended these

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						personal history of breast cancer and a BRCA1 or 2 mutation or at high risk of contralateral breast cancer. However, for women in this situation with no personal history of breast cancer there is no upper age limit. Breakthrough believes that women with a personal history of breast cancer should have access to at least as much surveillance as women without and would therefore recommend the removal of this upper age limit.	recommendations for consistency which now include the following Offer mammography as part of the population screening programme for all women aged 70 years and over with a personal history of breast cancer who: - remain at high risk of breast cancer (including those who have a BRCA1 or BRCA2 mutation, and - do not have a TP53 mutation'.
SH	Breakthrough Breast Cancer	29	Full	137	18	There are no recommendations for screening women with a TP53 mutation who have a personal history of breast cancer, whereas there are recommendations for screening women with a TP53 mutation without a personal history of breast cancer. Breakthrough believes that women with a personal history of breast cancer should have access to at least as much surveillance as women without and would therefore suggest that the recommendations for screening TP53 mutation carriers without a personal history of breast cancer be extended to TP53 mutation carriers with a personal history of breast cancer.	Thank you for your comment. We have now added a recommendation to 'Consider annual MRI surveillance for women aged 20-69 years with a TP53 mutation'. Although women with a TP53 genetic mutation were not included in the cost effectiveness review for this topic, the GDG agreed that they could extrapolate any relevant findings or conclusions from the population in section 6.2 (women without a personal history).
SH	Breakthrough Breast Cancer	30	Full	140	8	These recommendations (carried over from NICE clinical guideline 80) mean that women at moderate risk of developing breast cancer who have had breast cancer who are already old enough to enter the general population three-yearly screening programme should receive annual mammography for five years, after which they will go back to having mammograms every three years as normal. For younger women, annual mammography should continue until they are old enough to qualify for the	Thank you for your comment. The evidence was not reviewed for moderate risk women. However, GDG agreed that surveillance should be consistent with the recommendations that have already been produced as part of the NICE early breast cancer guideline (CG80) and reference to these has been included in the full

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						general population three-yearly screening programme. These recommendations mean that some moderate risk women with a personal history of breast cancer will receive less frequent screening from age 50-60+ than moderate risk women without a personal history of breast cancer, as the recommendations for moderate risk women without a personal history of breast cancer state that annual mammography should be considered for this age group. Breakthrough believes that women with a personal history of breast cancer should have access to at least as much surveillance as women without and would therefore suggest that the recommendations for screening moderate risk women unaffected by breast cancer be extended to affected women.	guideline, section 7.3.1. The relevant recommendation in CG80 states then when reaching 5 years of annual mammography the national screening programme will be expected to stratify screening frequency for people at moderate risk.
SH	Breakthrough Breast Cancer	31	Full	164	6	In general, people with, or with an interest in a family history of breast cancer replying to Breakthrough's February 2013 survey welcomed the recommendations on chemoprevention for women with a family history. In particular, they welcomed having an alternative risk reduction strategy other than surgery for people at high risk of breast cancer. *"I think it is positive that women are going to be offered an alternative to radical surgery which carries its own risks and is a huge psychological and physical challenge."* *"Having had surgery, an alternative would have been something I would have considered. This offers a less 'barbaric' way of addressing the risk."*	Thank you for this information.
SH	Breakthrough Breast	32	Full	164	6	Healthcare professionals and people with a family	Thank you for your comment.

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	Cancer					history of breast cancer have approached Breakthrough to ask whether chemoprevention can be effective in preventing ER-negative (in particular, triple-negative) disease. This point should be specifically addressed in the "Linking evidence to recommendations" section for these recommendations in order to clarify this point in cases where families have a history of ER-negative disease. Information on this subject should also be included in the patient version of the guidelines. *"I understand some BRCA gene faults are [associated with] triple negative, would these drugs be of any benefit to these women?"*	There was insufficient evidence of a specifically different effect in BRCA gene carriers, so the amended background notes the ER specific risk reduction. Therefore the recommendations have not been amended as the risks should be discussed on an individual basis
SH	Breakthrough Breast Cancer	33	Full	175	9	This aspect of the guideline has been met with mixed opinions by people with, or with an interest in a family history of breast cancer replying to Breakthrough's February 2013 survey. Some welcomed the recommendations for providing clarity on whether people with a family history of breast cancer who had had an oophorectomy could be offered HRT. Some stated that this would make it easier for patients who had undergone risk-reducing oophorectomy to manage menopausal symptoms, which in turn would make it easier for women to choose surgery as an option. *"It's good to have a recommendation based on proper research. Early menopause might stop some women who really ought to have surgery going for it - it did me. Being offered proper research and HRT would have given me a different decision."*	Thank you for your comment. We are pleased to hear this. Thank you.

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						However, some women were still concerned that taking HRT is an unacceptable risk for women with a family history of breast cancer, even when taken after oophorectomy. This indicates that widespread perceptions of the connection between HRT and breast cancer risk may be difficult to counteract. *"[I] would not be comfortable advising HRT given the increased risk of breast cancer."* The rationale for these recommendations therefore needs to be clearly explained both in the full guideline and in the patient version of the guideline. The choice whether or not to take HRT will always be a personal one but this choice should be based on an informed assessment of personal risks and benefits rather than false perceptions.	There is no evidence to suggest that HRT increases the risk of breast cancer in women under 50 who have had their ovaries removed and we hope that this guideline alleviates their concerns. The rationale for these recommendations is clearly explained in the linking evidence to recommendations section page 196, line 13 onwards. HRT should only ever be prescribed after an assessment of personal risks and consideration of benefits.
SH	Breast Cancer Campaign	1	NICE	3	2	The use of the term "related cancers" should be clarified in the first instance to specify which cancers are considered related. These cancers then need to be named/referred to as "related cancers" consistently throughout the guidelines.	Thank you, we have added examples.
SH	Breast Cancer Campaign	2	NICE	3	11	The sentence "the risk of developing breast cancer depends on" needs to be changed to either clarify that the risks listed are the key ones for people with a family history of breast cancer, or the wording changed to explicitly include non-familial risk factors such as lifestyle and environmental factors.	Thank you for your comment. We have amended the text to make its clearer that we are referring to familial breast cancer.
SH	Breast Cancer Campaign	3	NICE	3	24	There is an issue in assuming "that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients" when off-label recommendations are being used.	Thank you for your comment. This is standard text of the NICE version. We acknowledge the use of Tamoxifen for chemoprevention

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						For example there is no product characteristic summary for Tamoxifen that references its use in chemoprevention for breast cancer.	is outside of its license indication and this has been clearly referenced in the recommendations in the guideline. See full guideline, page 184, footnote 64.
SH	Breast Cancer Campaign	4	Full	5 & 26	5 & 33	"about one in five" is inconsistent with "6-19% of women with breast cancer will have a family history of the disease" we suggest "up to one in five".	Thank you for your comment. This section has been updated to now say 'up to one in five'.
SH	Breast Cancer Campaign	5	Full	164 7 (KPI)	 7	Only chemoprevention for **post**-menopausal women is mentioned in the key priorities and it is not clear why this is the case.	Thank you for your comment. The GDG are limited to 10 key priorities. The GDG used set criteria defined in the NICE guidelines manual (2012) to help them select their choices which are then voted upon. Unfortunately this recommendation was not selected.
SH	Breast Cancer Campaign	6	Full	13	40	We welcome the inclusion of three patient/carer members on the GDG.	Thank you.
SH	Breast Cancer Campaign	7	Full	22-25		Similar algorithms/flow charts were used in the previous quick reference guide and could be included in the NICE version of guidelines for ease of reference.	Thank you. We will forward your comments to the editorial team at NICE. The algorithms have also been updated in the full guideline to reflect any changes made to the recommendations in response to comments received from stakeholders.
SH	Breast Cancer Campaign	8	Full	26	42	The following statement is not referenced "About 5% of all breast cancers are largely attributable to inherited mutations in specific genes including BRCA1, BRCA2 and TP53."	Thank you for your comment. The references have now been added to the guideline.
SH	Breast Cancer Campaign	9	Full	27	27/28	We welcome the questionnaire of cancer geneticists and gynaecological oncologists, and are happy that current good practice has been incorporated into the guidelines. We would encourage the full report	Thank you for your comment, it is hoped that the full needs assessment will be published as a peer review article.

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						on these questionnaires (currently in the guidelines supplements) to be more publicised/available to improve the scientific literature in this area for the interest and use of the wider breast cancer and relevant genetic communities.	
SH	Breast Cancer Campaign	10	Full	30 and 38	4/5 and 12	The InCRisC study highlighted strong views amongst GPs against taking a reactive, instead of proactive, approach to seeking women with a family history of breast cancer but this has not been addressed in these guidelines. Further consideration is need on this issue.	Thank you for your comment. However, this is beyond the scope of the guideline.
SH	Breast Cancer Campaign	11	Full	37	5-6	In the text on the important features of family history, related cancers are listed as "other related early onset tumours such as ovary, pancreas, prostate, sarcoma and adrenal carcinoma". These cancers are then referred to inconsistently throughout the guidelines. For example, the algorithms on pages 22-25 mention "sarcoma" and "glioma" and "adrenal cortical carcicomas" separately but then encompass others in "complicated patterns of multiple cancers at a young age".	Thank you for your comment. We have amended this list (and the algorithm) to be more consistent with the recommendations on pages 69 and 70.
SH	Breast Cancer Campaign	12	Full	85	10	We welcome the recognition that individuals at high risk may have no available family member for genetic testing and should therefore be offered testing at the guideline recommended thresholds. We also welcome all other recommendations on genetic testing including "Clinical genetics laboratories should record gene variants of uncertain significance, periodically review for evidence of causality and ensure that families are contacted as appropriate" and commend the GDG for the development of a thorough economic model on which to base this decision as well as incorporating current best practice from the cancer	Thank you Thank you for your comments on the economic model as well as our decision to include data from the needs assessment survey. We have amended and expanded this recommendation to include advice on the potential risk and benefits of genetic testing and

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						geneticists survey.	inform families with no clear genetic diagnosis that they can request review in the specialist genetic clinic at a future date. The recommendation no longer recommends that clinical genetics laboratories should ensure families are contacted or that laboratories should periodically review for evidence of causality as it was agreed this is not the responsibility of the laboratory.
SH	Breast Cancer Campaign	13	Full	61	35-36	We welcome the recognition of a need to test for PTEN and E-cadherin mutations where clinically appropriate. But think this could be mentioned within recommendations, for example "testing should be considered for PTEN and E-cadherin mutations where clinically appropriate"	Thank you for your comment. These are very rare mutations and therefore were not prioritised for inclusion in this guideline.
SH	Breast Cancer Campaign	14	Full	86	12/13	We welcome the decision to avoid age inequality in genetic testing for people over 60.	Thank you.
SH	Breast Cancer Campaign	15	Full	43 8 (KRR)	 4 - 15	We welcome the recognition of the need for more research to improve accuracy of carrier probability models but are concerned that the recommendation only focuses on BRCA mutations.	Thank you for your comment. These calculation methods are only capable of estimating BRCA gene mutation probability.
SH	Breast Cancer Campaign	16	Full	92 8 (KRR)	 18 - 36	We welcome the research recommendation concerning rapid genetic testing for current breast cancer patients and hope that this can be addressed quickly so that any resulting necessary changes to services can be rapidly implemented. The Clinical Molecular Genetics Society (CMGS) audit raises the issue that test reporting times do not always reflect how long a patient waits for results (pg 28 line 47/48) so this needs to be incorporated into this recommendation so that a	Thank you for your comment. We would hope that the issue of time to notification of results would be assessed as part of on-going research.

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						patient hears results within 4 weeks, rather than tests being carried out within 4 weeks.	
SH	Breast Cancer Campaign	17	Full	96	1-2	We welcome the recommendation for consideration of the psychological impacts of fast track genetic testing, as well as the need to assess who should discuss testing within the multidisciplinary team. This recommendation should be added to the NICE summary guidelines to give a complete picture of what is needed from research into rapid genetic testing.	Thank you for your comment. Only the top 5 research recommendations appear in the NICE guideline. This research recommendation was not prioritised by the GDG for inclusion.
SH	Breast Cancer Campaign	18	Full	166 9 (KRR)	 1 - 12	We would welcome the results from this research into Tamoxifen vs aromatase inhibitors and hope that the guidelines would be updated as quickly as possible to reflect the results from relevant trials.	Thank you for your support.
SH	Breast Cancer Campaign	19	Full	181 9 (KRR)	 15-25	Research will also need to be done on the psychosocial and clinical outcomes for women who choose and women who do not choose to take chemoprevention drugs. Also research on risk-reducing surgery outcomes will have to take into consideration whether women had the option of chemoprevention.	Thank you for your comment. A significant amount of research has already been carried out in this area therefore we do not believe any additional research would be beneficial.
SH	Breast Cancer Campaign	20	Full	188	7	We welcome the recommendation to assess the risks and benefits of radiotherapy and chemotherapy for people with a TP53 mutation and hope that this information will help TP53 mutation carriers with other cancers too.	Thank you.
SH	Breast Cancer Campaign	21	Full	116-117		The guidelines have not considered the link between breast cancer risk and breast density on mammography. We feel a valid research recommendation would be a study to find out what breast density could tell us about breast cancer risk in women with a family history of breast cancer	Thank you for your comment. We have made a research recommendation for women with a personal history of breast cancer. See page 160.
SH	Breast Cancer Campaign	22	Full	116	all	Known TP53 carriers and women with a greater than 30% TP53 carrier probability are not being offered annual mammography at 50 years, whereas known BRCA1/2 carriers are. The reasoning for this	Thank you for your comment. We have made this clearer in the LETR paragraph.

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						may be that women with TP53 mutations are likely to develop breast cancer before age 50 (as highlighted on p61 lines 27-28), but we would like to see the reasoning and evidence on this outlined clearly, and separately, for women who are TP53 carriers as well as those with a 30% carrier probability risk	
SH	Breast Cancer Campaign	23	Full	116	all	There needs to be a written line in the recommendations that women aged over 50 at high risk who do not fit into the BRCA1/2 or TP53 carrier classifications should be offered annual mammography. Currently this is only shown in the table on pg 118 and not explicitly mentioned in the guidelines.	Thank you for your comment. We believe this is made clear by the recommendation 'Offer annual mammographic surveillance to all women aged 40 years and over at high risk of breast cancer'.
SH	Breast Cancer Campaign	24	Full	30	47/48	The questionnaire of cancer geneticists has highlighted the variability of MRI provision due to lack of local resources. A lack of MRI availability for MRI surveillance is extremely concerning and there should be appropriate investment and planning to ensure commitments in these guidelines are delivered.	Thank you for your comment. We agree. These are also key issues for implementation and will be highlighted to the Implementation Team at NICE
SH	Breast Cancer Campaign	25	Full	31	5	Ovarian screening is not addressed by these guidelines although there is a link between family BRCA mutations and a higher risk of both breast and ovarian cancer. It's noted that about half of the gynaecological oncologists surveyed have continued offering ovarian screening outside the UK FOCSS trial.	Thank you for your comment. However it is beyond the scope of the guideline to comment on how gynaecological oncologists manage ovarian cancer risk. Ovarian surgery, including recommendations on discussing the risks and benefits are covered elsewhere in the guideline (please see sections 8.3.2. and 8.3.4).
SH	Breast Cancer Campaign	26	Full	164	6	Has the guideline development group considered the inclusion of different recommendations for women who are at increased risk of endometrial cancer (as opposed to having a personal history of endometrial cancer) and so should not be offered	Thank you for your comment. We have amended the recommendations to take into consideration women at increased risk of endometrial cancer.

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						Tamoxifen/raloxifene?	
SH	Breast Cancer Campaign	27	Full	156	11	There has been an update to this evidence – Vogel et al 2006 – which does not appear to have been taken into consideration - Vogel et al. 2010 Cancer Prev Res 3(6):696-706	Thank you. Vogel 2010 has been added and the evidence statements and tables have been amended accordingly.
SH	Breast Cancer Care	1	Full	164 7 (KPI)	5	**Key priorities - Chemoprevention** There is no mention of offering tamoxifen to pre-menopausal women at high risk of breast cancer as outlined in the recommendations on page 164. This is a significant change to present options and should be acknowledged in the key priorities alongside post menopausal chemoprevention. **Note of interest**: when this draft initial came out majority of media interest was on chemoprevention for pre-menopausal women – indicating of importance.	Thank you for your comment. The GDG are limited to 10 key priorities. The GDG used set criteria defined in the NICE guidelines manual (2012) to help them select their choices which are then voted upon. Unfortunately this recommendation was not selected.
SH	Breast Cancer Care	2	Full	164 7 (KPI)	11	**Key priorities - risk-reducing surgery for women with a personal history of breast cancer**. This is a significant consideration for women with a personal history of a suspected (high risk) or known hereditary breast cancer. At Breast Cancer Care, women using our support services tell us how difficult it can be preceding with both risk-reducing mastectomy to the contra-lateral breast and bilateral salpingo-oophorectomy, particularly if their cancer is oestrogen receptor negative. The women who use our services also highlight that it isn't unusual for them to be the one who initiates any risk-reducing surgery discussions with their oncologist. Now that it is recognised formally with supporting evidence of need and recommended for discussion and consideration on page 180, Breast Cancer Care believes it should be highlighted within the key	Thank you for your comment. The GDG are limited to 10 key priorities. The GDG used set criteria defined in the NICE guidelines manual (2012) to help them select their choices which are then voted upon. Unfortunately this recommendation was not selected.

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						priorities as it is a significant factor to consider the ongoing care of women with a suspected (high risk) or known hereditary breast cancer.	
SH	Breast Cancer Care	3	Full	32	15 & 16	Breast self examination was replaced with a breast awareness (BA) model of care in 1991. The BA model was reinforced as best practice (supported by evidence) in: 1995, 2002 and by the Cochrane Review Group in 2003 Therefore can this sentence say breast awareness in place of breast self-examination **Ref:** Kosters JP, Gotzsche PC (2003) Regular self-examination or clinical examination for early detection of breast cancer. *Cochrane Database of Systematic Reviews Issue 2.*	Thank you for your comment. We have made this change to the needs assessment.
SH	Breast Cancer Care	4	Full	91	41	The guidance says the GDG felt the current pathway gives patients time to make an informed choice as to whether to be referred or not. However, this group has just been diagnosed with breast cancer at a very young age with no obvious family history, therefore their situation is very different and it shouldn't be assumed their needs will be the same. At Breast Cancer Care we hear form many young women attending our younger women support forums, with a huge need to understand why they have been diagnosed so young and its implications. They want to utilise all treatment options as soon as possible, so as to maximise living a long life. These young women say they don't want possible treatment options withheld from them, because there is a concern that they were being given too much information too quickly or there is concern they may make decisions in haste.	Thank you for your comment. We agree that it is important to fully inform people of all the treatment options available, however there is no evidence that rapid genetic testing improves long term outcomes for these women.

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						Young women want to be part of the decision making process. Therefore that means being given **All** the information as soon as is possible, so they are equipped to make a thorough individual informed choice. Evidence shows women with an inherited breast cancer (BRCA1 BRCA2) have the biggest increased risk of contra-lateral breast cancer over other women diagnosed with breast cancer (Malone et al 2010). At Breast Cancer Care we know from users of our discussion forums, they openly discuss current evidence amongst each other. Therefore for some young women, the importance of knowing if their breast cancer diagnosis is due to an altered gene mutation, at the earliest possible time frame, can not be underestimated. So saying the current pathway is suitable would not be a true reflection in all cases. **Refs:** • Malone K et al (2010) Population- based study of the risk of second primary contralateral breast cancer associated with carrying a mutation in BRCA1 and BRCA2. *Journal of Clinical Oncology 28, 14, 2404-2410*	
SH	Breast Cancer Care	5	Full	91	43 & 44	The guidance says, it was noted that fast track referral may limit the options in terms of choice of surgeon and reconstructive procedures. Choice in surgeon preference and reconstruction types is an issue for any woman diagnosed with breast cancer that is advised to have mastectomy	Thank you for your comment. Potentially limiting the options in terms of choice of surgeon and

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						and was highlighted in the National Mastectomy and Breast Reconstruction Audit report (NHS Information Centre 2010), The statement suggests it is a 'unique' reason against fast tracking for genetic testing within 4 weeks of a diagnosis of breast cancer. Also this statement could suggest a different pathway of care for suspected (high risk) or confirmed hereditary breast cancer, as it is not in line with the NICE clinical guidance 80 (2009) recommendations - all women who are advised to have a mastectomy, to discuss immediate reconstruction and all the different types of reconstruction whether they are all available locally **Ref:** • National Mastectomy and Breast Reconstruction Audit (2010). *The NHS IC*	reconstructive procedures was not the only reason for not recommending fast track referral for genetic testing. Patients will also need time to make an informed choice to be referred or not, allow them time to discuss it with their families and the implications of a mutation potentially being detected. This is all included in the LETR paragraph on page 119. Because there was no evidence that a delay in genetic testing at diagnosis of breast cancer affected overall survival the GDG were not able to recommend rapid genetic testing. Therefore we have amended the recommendations to say 'Offer fast track genetic testing (within 4 weeks of a diagnosis of breast cancer) only as part of a clinical trial.' The recommendations in CG80 refer to the management of breast cancer by mastectomy and immediate reconstruction not the use of risk reducing surgery.
SH	Breast Cancer Care	6	Full	87-91		**Re: Rapid genetic testing within 4 weeks of being diagnosed with breast cancer pages 87-91.** At breast Cancer Care we hear from many young women who have just been diagnosed with breast cancer. They discuss many issues including fear of	Thank you for your comment. We understand the enormous concerns faced by women on

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						another breast cancer in the other breast. They do discuss surgery to the other breast very early on in their diagnosis	receiving a diagnosis of breast cancer and the fear of subsequent cancer in the other breast. We hope these guidelines can provide some advice on surgery for those women with a family history.
						Many of our users on our discussion forums discuss triple negative breast cancer and potential of being BRCA1 and genetic testing. Examples of two different discussions below http://www.breastcancercare.org.uk/community/forums/triple-negative-brca1-link http://www.breastcancercare.org.uk/community/forums/press-release-under-50-tnbc-should-be-offered-brca1-test	Thank you for this information.
						To only consider using the rapid access as part of a trial or if a woman is of Jewish origin (page 92 lines 4&5) will be seen as very unfair by a lot of young women whose breast cancer is triple negative, especially when the practice of rapid testing may continue in some hospitals. A confirmed BRCA genetic test result will have enormous implications and further considerations to their present treatment plan, which is why a great many of our users to our support services will see it as an important test, that should still be offered when appropriate, as quickly as possible.	The guideline makes it clear that genetic testing can be offered at any point in time to people with breast cancer who fulfil the referral criteria, including during the course of primary breast cancer treatment. There is no evidence of any benefit of rapid genetic testing for people newly diagnosed with breast cancer, and therefore a research recommendation was made to address this gap. Additionally the GDG could not support a recommendation to offer rapid testing on a widespread basis as the systems are not in

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							place to support this. Whilst it was acknowledged that identification of a BRCA1/2 mutation could have significant impact on the choice of primary treatment, a high proportion of triple negative breast cancers now receive neo-adjuvant chemotherapy which allows much more time for test information to be properly assimilated.
SH	Breast Cancer Care	7	Full	116-117		**RE: Surveillance for early detection of breast cancer pages**116-117 At breast Cancer Care we have heard from many women over the years who have found access to MRI as part of their annual surveillance difficult. We are now concerned that these new surveillance recommendations won't be easily or readily implemented nationally. Breast Cancer Care is very concerned that the **consider** surveillance for those at a moderate risk is likely to result a variation of care with different local protocols. A variation in care, as a result of different local protocols, could possibly have huge impact on	Thank you for your comment. This is an implementation issue and will be highlighted to the Implementation Team at NICE 'Offer' is appropriate wording for a recommendation where the GDG is confident that, for the vast majority of people, the recommendation will do more good than harm. 'Consider' is the appropriate wording for a recommendation where the benefit is less certain and where a discussion about risks and benefits is required. Inevitably this may result in inconsistencies of practice that will reflect patient choice. We agree, and the aim of these guidelines is to reduce the

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						families who are living in different parts of the country from each other - one sibling is advised to have an annual mammograms and the other not.	variation in practice across the UK.
SH	Breast Cancer Care	8	Full	137		**Re: Surveillance recommendations for women with a personal history of breast cancer page 137** Since 2006 when the present guidelines advised annual MRI surveillance for women at high risk and confirmed BRCA1/2 gene carriers, access to MRI hasn't been readily available nationwide and for some not at all. Breast Cancer Care is concerned that these new recommendations for women with a suspected (high risk) or confirmed hereditary breast cancer aged 30-49, will result in further difficulties of access once again. Breast Cancer Care believes incorporating these recommendations into the NICE Clinical guidance 80 (2009) is extremely important in order for these recommendation to be adhered to. An update of the NICE clinical guidance 80 (2009) was scheduled for 2012. However, there was a consensus that there was no new evidence that would impact or change the current clinical practices. NICE states; **"If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations"** http://publications.nice.org.uk/early-and-locally-advanced-breast-cancer-cg80/updating-the-guideline	Thank you. We have crossed referred to CG80 where appropriate and we will pass your comments onto the NICE CCP review team for when CG80 is next reviewed for update.

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						These recommendations do significantly affect follow-up care of women with a suspected (high risk) or confirmed hereditary breast cancer with different recommendation for 30-49 and 50 yrs and older. In addition to women knowing their risk status at the time of their breast cancer diagnosis. Breast Cancer Care hear from a number of woman where their family history isn't known or asked for when they are first diagnosed with breast cancer. Many women don't receive confirmation of their high risk, BRCA 1, BRCA2 or TP53 status until after all treatments has been completed – these new guidelines will impact on their follow-up care. Therefore the importance of assessing/ enquiring about family history, at the time of a breast cancer diagnosis, should also be added to the NICE clinical guidance 8 (2009)	
SH	Breast Cancer Care	9	Full	155	39 - 42	The guidance states "In the adjuvant setting Raloxifene is only effective in postmenopausal women, but can increase the risk of osteoporosis and bone fractures…" This is incorrect Raloxifene is not used to treat breast cancer and it doesn't increase the risk of osteoporosis and bone fractures. It is used as a treatment for osteoporosis and helps protect from the risk of bone fractures Did you mean to explain the role and contradictions of exemestane or aromatase inhibitors in general as adjuvant treatment?	Thank you for pointing out these errors in the background text. These errors have been corrected.
SH	Breast Cancer Care	10	Full	155-164		**Re: Chemoprevention for women with no personal history of breast cancer pages 155-164**	Thank you for your comment. We agree that this is a difficult area

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						Breast Cancer Care is very aware from our users of all of our services that taking tamoxifen is not simply 'just a tablet' Many women experience long-term and severe side effects, but 'put up with it' because of their breast cancer diagnosis, whilst other will stop as they can not tolerate the side effects anymore. Hershman and colleagues (2010) and Murphy and colleagues (2012) highlight the compliance issues of hormonal therapy for breast cancer and increased risk of recurrence as a result of non-compliance. Breast Cancer Care would like to highlight the importance of women understanding the risks and benefits of chemoprevention, so they can make an informed choice about which option is best for them. Should tamoxifen and raloxifene be recommended in the final guidance, all eligible women should be informed they do not have a UK license and would be given off-label, that side effects of varying severity (mild to severe) and duration can occur, and that anyone taking the chemoprevention should continue to be monitored throughout, with clear instructions about who to report new or worsening adverse effects to. Once again, Breast Cancer Care is very concerned that the **consider** chemoprevention for those at a moderate risk is likely to result a variation of care with different local protocols. A variation in care, as a result of different local protocols, could possibly have huge impact on families who are living in different parts of the country from each other - one sibling is advised to take tamoxifen or raloxifene and the other sibling	however there was high quality evidence of breast cancer risk reduction with tamoxifen and raloxifene. The "offer" recommendation for high risk women and the "consider" recommendation for moderate risk women take account of the balance between benefit and risk and side effects. There needs to be an informed discussion with each woman about the risks and benefits. This means there could be variable uptake even within the same family.

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						isn't. **Ref**: Hershman D L et al (2010) Early discontinuation and nonadhererenceto adjuvant hormonal therapy in a cohort of 8,769 early-stage breast caner patients. *JCO 28, 27, 41204128* Murphy C C et al (2012) Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review. *Breast Cancer Research and Treatment, 134,2, 459-478*	
SH	Breast Cancer Care	11	Full	176-180		**Re: Risk-reducing surgeries for women with a personal history of breast cancer pages 176-180**. Breast Cancer Care would like to highlight the importance of this recommendation being mentioned in an updated version of the NICE guidance 80 (2009) along with the follow-up care of women with suspected (high risk) or confirmed hereditary breast cancer.	Thank you for your comment. These recommendations refer to people with a personal and family history of breast cancer. The EBC guideline does not specifically consider this population.
SH	British Association of Surgical Oncology	1	Full	24, 25		In general the management algorithms are too small and too detailed, especially that for secondary and tertiary care to be useable and are worse than the ones in the previous version, which have caused a lot of confusion over the past 6 years. These should be simplified if possible or split into separate algorithms	Thank you for your comment. We have simplified each algorithm, removed any duplication and tried to make the text larger and more 'user friendly'. We have presented separate pathways within each algorithm for people with and without a personal history of breast cancer. The algorithm has also been updated to reflect any changes made to the recommendations, and in response to comments received

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							from stakeholders.
SH	British Association of Surgical Oncology	2	Full	all		In general the literature reviews are of very high quality and the review team should be commended for producing an excellent body of work	Thank you.
SH	British Association of Surgical Oncology	3	Full	164		I wonder if some guidance on how tamoxifen use should be rolled out. We have kept a data base for the last 10 years of all our high risk women and could either write to the GPS or the patients inviting them to discuss this. This would have major implications for workload. Specific recommendation that this should be retrospective to women already referred for risk management will encourage commissioners to release funds for the admin costs etc of this.	Thank you for your comment. This is an implementation issue and will be highlighted to the Implementation Team at NICE.
SH	British Association of Surgical Oncology	4	Full	116		Additional annual mammograms in high risk women are welcome. However, this is a huge workload if units are expected to change their intervals retrospectively or just use the new guidelines for new referrals. It might be useful to state implicitly that this should apply retrospectively so commissioners feel they can free up funds for all the admin costs identification and case finding and checking and notification may entail	Thank you for your comments. Provision of additional mammograms in this population group is an implementation issue and will be highlighted to the Implementation Team at NICE We acknowledge that implementation of these guidelines will have implications for people undergoing additional surveillance under current protocols and it will be necessary to consider means of re-contacting this group of people to ensure that where appropriate, they are able to be access the updated surveillance protocols. We have added additional text in section 7.2 of the full guideline to clarify this.
SH	British Association of Surgical Oncology	5	Full	64 (Old)	9	Extending availability of genetic testing to very high risk women with no live affected relative is welcome	Thank you for your comment.

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				85 (New)		and will plug a major gap in equity in this group of women who often have lost their mother at a very age and therefore are denied the test.	
SH	British Association of Surgical Oncology	6	Full	75 and other places		I do not think it is helpful to show tables of ICERS to non experts with no experience of health economics and all of this hyper detailed health economics should be taken out of the full guidelines. A simple statement that XXX becomes cost effective at XX level of risk is sufficient. Similarly the cost per qaly tables should be left out and simple statements put in	Thank you for your comment. The full guideline only presents a summary of the results of the health economic modelling. It is generally considered good practice to report ICERs as they are a crucial part of health economic analysis and we would be reluctant to remove the tables from the full guideline. Short summary statements are provided below every table for better understanding.
SH	British Association of Surgical Oncology	7	full	91		Increasing availability of next generation sequencing facilities up and down the UK means that a fast track result may well be available and will have a material potential impact on cancer care. In particular a woman found to be a gene carrier who initially decides to have a WLE and RT may have their subsequent options for a skin sparing mastectomy compromised by undergoing RT. I therefore think that this should be advised as an aspiration to all high risk women where risk of gene carriage is substantial. I have had several women whose subsequent gene carrier status made them request RRS and whose reconstruction options were limited as a result.	Thank you for your comment. The guideline makes it clear that genetic testing can be offered at any point in time to people with breast cancer who fulfil the referral criteria, including during the course of primary breast cancer treatment. There is no evidence of any benefit of rapid genetic testing for people newly diagnosed with breast cancer, and therefore a research recommendation was made in order to address this gap.
SH	Cancer Genetics Group		full NICE	91 1.5.16		"Offer people eligible for referral to a specialist genetics clinic a choice of accessing genetic testing during initial management or at any time thereafter" This seems to be contradictory to 1.5.15, which is	Thank you for your comment. We disagree that the recommendation is contradictory. Bullet 1 gives a precise and short time limit (within 4 weeks of diagnosis) whereas the

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						recommending that patients are not referred to genetic testing during initial management. Further clarification is required	second recommendation allows time for early referral and consideration of testing. However we have re-ordered these recommendations so that the choice of accessing genetic testing during initial management or at any time thereafter comes before the offering fast track testing only as part of a clinical trial.
SH	Cancer Genetics Group	1	Full	general		This proforma is difficult as there are no line numbers on the NICE version but only numbered paragraphs. I have used these for comments on the NICE version. The recommendations in the full version also do not have line numbers. I have therefore only used page numbers and have correlated the comments in both the NICE and full version.	Thank you for your comments. We will pass your concerns regarding the proforma to the Centre of Clinical Practice team at NICE.
SH	Cancer Genetics Group	2	Full	general		Overall these guidelines are welcomed and are of use to the cancer genetics community, in particular with regard to those women who have a personal history of breast cancer. Previously the guidelines excluded this category. The general category of "consider" is felt to be unhelpful and is likely to lead to inequity of service across the country. Each service will need to decide whether to act on the "consider" categories, which will be influenced by local economic issues. For regional genetic services, the workload will be considerably increased if all "consider" categories are acted upon and this may actually be in conflict with referral criteria which are due to be audited against by the National Commissioning Board as part of the CQUINs scheme 2013/2014. **We strongly suggest the removal of the**	Thank you 'Offer' is appropriate wording for a recommendation where the GDG is confident that, for the vast majority of people, the recommendation will do more good than harm. 'Consider' is the appropriate wording for a recommendation where the benefit is less certain and where a discussion about risks and benefits is required. Inevitably this may result in inconsistencies of

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						"consider" category from the guidelines	practice that will reflect patient choice.
SH	Cancer Genetics Group	3	Full NICE	85 1.5.8 1.5.9 (85)		"offer genetic testing in tertiary care" "consider genetic testing in tertiary care" Tertiary care needs clarifying – if all genetic testing is to be undertaken within the Regional Genetic Services, changing the cut off for genetic testing will substantially increase the workload into these services and potentially conflict with national referral guidelines for only high risk individuals to be seen in the Regional Genetic Services. This may cause a conflict with the National Commissioning Board's commissioning of medical genetics. If tertiary care is to include oncology/surgical services, recommendations about the information given to women need to be more explicit and funding streams for genetic testing within these specialised services need to be established. There also needs to be guidance to these services regarding confirmation of diagnosis prior to testing. Add in the Manchester Score – 12-15 (for probability of 5-10%)	Thank you for your comment. We have amended these recommendations for simplicity, and changed the term 'tertiary care' to 'specialist genetic clinics'. This is also an implementation issue and will be highlighted to the Implementation Team at NICE We have removed reference to the Manchester Score from the guideline as it is one of several methods of providing an estimate of probability of finding a mutation, and therefore no does warrant being given special attention. The model was based on a percentage threshold which we have retained for consistency.
SH	Cancer Genetics Group	4	full NICE	85 1.5.11		10-20% probability equates to Manchester Score 15-17	We have removed reference to the Manchester Score from the guideline as it is one of several methods of providing an estimate of probability of finding a mutation, and therefore no does warrant being given special attention. The model was based on a percentage threshold which we have retained for consistency.

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SH	Cancer Genetics Group	5	Full NICE	85 1.5.13		Add in Manchester score of 12-15 for 5-10% probability	We have removed reference to the Manchester Score from the guideline as it is one of several methods of providing an estimate of probability of finding a mutation, and therefore no does warrant being given special attention. The model was based on a percentage threshold which we have retained for consistency.
SH	Cancer Genetics Group	6	full NICE	85 1.5.14		"Clinical genetic laboratories should record gene variants of uncertain significance, periodically review for evidence of causality and ensure that families are contacted as appropriate" It is not the responsibility of clinical laboratories to contact families with genetic testing results. This is the responsibility of the clinicians requesting testing. Clinicians should, when reviewing individuals, undertake an assessment of the variant and if necessary discuss with laboratory colleagues before taking a clinical decision as to whether to inform the family of any potential change in status of the variant. The guidance is open-ended and open to wide interpretation. For example, the frequency of review is unclear, should it be every 1, 2 or 5 years? Local policies may be open to challenge without more concrete guidance. It is also unclear at to which category change should be notified as	Thank you for your comment. We have amended and expanded this recommendation to include advice on the potential risk and benefits of genetic testing and inform families with no clear genetic diagnosis that they can request review in the specialist genetic clinic at a future date. This recommendation has been revised and it no longer recommends that clinical genetics laboratories should ensure families are contacted.

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						laboratories use a system of categories that are subjective and require professional judgment in their application. For example, would contacting families only apply where a variant is reclassified from any other category to 'definitely pathogenic'. What if a variant is reclassified as 'probably pathogenic', potentially important information for the family but not necessarily actionable. Equally, evidence can arise that re-classifies variants as less likely to be pathogenic. Will there be a duty to also inform families when a variant changes from 'pathogenicity unknown' or 'probably pathogenic' to 'unlikely to be pathogenic'? Classifications used by different clinical laboratories although similar are not equivalent and there will be different classifications applied by different laboratories to the same variant leading to potentially different branches of the same family being given conflicting information on the same variant. Although this is no different to the situation at reporting now, regular review will lead to more families being given conflicting information particularly as reviews between centres are unlikely to be synchronised. The process of reviewing evidence is laborious and time consuming. Currently, this process takes a Clinical Scientist 1-2 hours per variant. Within the last 18 months in Manchester, 483 samples were screened and 64 unclassified variants identified, the majority of which are rare variants unlikely to be observed more than once by the same centre. Over time, therefore the list of unclassified variants will increase (especially if offering mutation screens to larger numbers of individuals). Using current methods, reviewing the evidence for 100 UVs will	

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						take 150 hours of a clinical scientists time; a minimum of one month of a 1.0 WTE Clinical Scientist time. This statement would set a huge precedent within the laboratories. Mutation screening for BRCA1/2 is a small part of the workload for regional genetic laboratories. If regular review of UVS is required for these genes, it would be needed for all genes screened which would become untenable. The responsibility for reassessing variants and contacting the families should lie with the clinicians requesting testing. This will require education of the non-geneticists requesting genetic tests. **We strongly suggest that this statement is removed from the guidelines**.	
SH	Cancer Genetics Group	7	full NICE	91 1.5.15		**"**do not offer fast track genetic testing……except as part of a clinical trial" There are a handful of clinical situations in which fast track testing may impact upon clinical management of an individual undergoing treatment for breast/ovarian cancer. For example, - the decision regarding treatment of DCIS may be altered with knowledge of BRCA1/2 status. **We would suggest that this statement be altered to allow testing on a case-by-case basis following discussion with the local consultant cancer geneticist**.	Thank you for your comment. The guideline makes it clear that genetic testing can be offered at any point in time to people with breast cancer who fulfil the referral criteria, including during the course of primary breast cancer treatment. There is no evidence of any benefit of rapid genetic testing for people newly diagnosed with breast cancer, and therefore a research recommendation was made in order to address this gap. Additionally the GDG could not support a recommendation to offer rapid testing on a widespread basis as the systems are not in

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							place to support this. Whilst it was acknowledged that identification of a BRCA1/2 mutation could have significant impact on the choice of primary treatment, a high proportion of triple negative breast cancers now receive neo-adjuvant chemotherapy which allows much more time for test information to be properly assimilated.
SH	Cancer Genetics Group	8	full NICE	116 1.6.3		"Offer annual mammographic surveillance to all women aged 40 years and over at high risk of breast cancer " It would be helpful to have an upper age limit.	Thank you for your comment. The GDG have revised the recommendations to clarify the age ranges where surveillance should be available for all the moderate and high risk groups. The GDG have acknowledged in the guideline that there was no evidence specifically relating to surveillance for women aged 70 years and over and could therefore make no specific, evidence-based recommendations. However, the GDG agreed that as these women remained at risk of breast cancer, they should still have access to surveillance. In the absence of any evidence to support enhanced surveillance, the GDG agreed that the best course of action was to recommend that these women should remain in or return to the standard population screening programme.
SH	Cancer Genetics Group	9	full	116		"Offer annual mammographic surveillance to	Thank you for your comment. We

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			NICE	1.6.4		women aged 30-39 years at moderate or high risk of breast cancer only as part of an approved research study" This is different from the previous guidelines which also allowed screening as part of an approved and audited system. Many women who are now in that audited system may need to be removed from screening. The only currently available study is due to stop recruiting in June 2013. **We suggest continuing with the previous guidelines**	disagree. We have revised this recommendation to now say 'Do not offer mammographic surveillance to women aged 30 - 39 years at moderate risk of breast cancer. This is because the risk of breast cancer in the moderate risk group is low and there continues to be a concern of the potential harm of radiation to young breast tissue and the incidence of radiation-induced cancers. We have added additional information in the LETR paragraph.
SH	Cancer Genetics Group	10	full NICE	116 1.6.9		"offer annual MRI surveillance to all women……aged 30-39 years who have not had a genetic test but are at greater than 30% probability of being a *BRCA1* carrier." This revision to the guidelines have removed the agreement for women at a 10 year >8% aged 30-39 years and at a 10 year >20% risk (12% with dense breasts) aged 40-49 years for MRI surveillance. This has particular impact on those women at 50% risk of inheriting a *BRCA2* mutation in a high penetrance family. By only allowing MRI surveillance to mutation carriers, this policy forces women into genetic testing. This is in direct opposition to non-directive genetic counselling which does not force a patient into testing when they may be psychologically unready to cope with results. **We strongly suggest that the original statement on risk equivalence is retained in the guidelines.**	Thank you for your comment. This recommendation remains unchanged from the 2006 guideline, and there is no new evidence to support a change. This category was included because there was a suggestion that women should be encouraged to undertake genetic testing in order to qualify for MRI surveillance. The numbers of women in this category are very small.
SH	Cancer Genetics Group	11	Full	118 (table		"Group 3 Untested but at greater than 30% BRCA1 carrier probability"	Thank you for your comment. The recommendation covers both

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				7.5)		Is this greater than 30% probability in a completely untested family or in untested woman in a known mutation family? Please clarify. Comments as for 1.6.9 also apply here	populations.
SH	Cancer Genetics Group	12	full NICE	137 1.6.12		"Offer annual MRI surveillance to all women aged 30-39 years with a personal history of breast cancer who are at high risk of contralateral breast cancer or have a *BRCA1* or *BRCA2* mutation" Define high risk	Thank you for your comment. We define 'high risk' in chapter 2 of the full guideline.
SH	Cancer Genetics Group	13	full NICE	137 1.6.13		''Offer annual mammographic surveillance to all women age 50-69 years with a personal history of breast cancer who are at high risk of contralateral breast cancer or have a BRCA1/2 mutation '' The age at which mammography screening commences and ends surely should be the same for women with and without a personal history of breast cancer if they have a BRCA1/2 mutation	Thank you for your comment. We have amended these recommendations for consistency.
SH	Cancer Genetics Group	14	full NICE	164 1.7.20		"Healthcare professionals within a specialist genetics clinic should discuss and give written information on the absolute risks and benefits (including side effects of drugs and the extent of the risk reduction) of all options for preventative treatment to women at high risk for breast cancer" Many women, referred to regional genetic services, are counselled about their breast cancer risk by genetic counsellors. Genetic counsellors often have a science degree or nursing background and have not had specific training regarding pharmacology. It is therefore unreasonable to expect them to discuss risk and benefits of the use of (currently) unlicensed drugs. **We suggest that the statement should be**	Thank you for your comment. This is an implementation issue and will be highlighted to the Implementation Team at NICE

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						modified to state that discussions around prevention should be available within a service.	
SH	Cancer Genetics Group	15	full NICE	164 1.7.21 1.7.22		"Offer tamoxifen for 5 years to pre-menopausal women at high risk of breast cancer unless they have a past history of thromboembolic disease or endometrial cancer" "Offer tamoxifen or raloxifene for 5 years to post menopausal women ……. or endometrial cancer" There needs to be an age range stated here. Tamoxifen should not be offered to young women in their 20s. There needs to be clear guidance on who is expected to prescribe this drug. It is felt that it would be inappropriate for this to be undertaken within the regional genetics services (many individuals are not seen by a doctor) as the workload increase would be large. The inevitable queries regarding compliance, side-effects etc need to be handled via the GP and a national information leaflet (possibly produced by NICE) is needed. This also raises the question of whether a risk assessment needs to be undertaken following prescription of tamoxifen and whether some women would then fall below the threshold for annual surveillance.	Thank you for your comment. The GDG agreed not to set a minimum age limit for accessing tamoxifen or raloxifene, as they did not want to prevent young women from having access to preventative treatment as there may be some who wish to discuss options other than risk reducing surgery. This is an implementation issue and will be highlighted to the Implementation Team at NICE. Chemoprevention is attempting to reduce risk but it impossible to measure any reduction on an individual basis.
SH	Cancer Genetics Group	16	full NICE	164 1.7.25 1.7.26		As 1.7.21	Thank you for your comment. The GDG agreed not to set a minimum age limit for accessing tamoxifen or raloxifene, as they did not want to prevent young women from having access to preventative treatment as there may be some who wish to discuss options other

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							than risk reducing surgery.
SH	Cancer Genetics Group	17	Full	23		Algorithm "Care and management of people in primary care with a personal history of breast cancer" 6th central box – bullet point 2 "Referral to tertiary care for individual with triple negative breast cancer or medullary breast cancer before 50". This is in contradiction to 1.4.5 (NICE) which suggests referral if triple negative tumour diagnosed under 40 years. This algorithm suggests direct referral to the tertiary services if any of the criteria are filled. It should be the same as the care for women without a personal history. **We suggest that the algorithm is altered to suggest that if the criteria are filled, advice is sought from the tertiary centre.**	Thank you for bringing this to our attention. This was an error in the algorithm which we have now corrected. The recommendations that cover this topic clearly state a triple negative breast cancer under the age of 40 years¸ as there is no strong evidence for sporadic TNT at aged 40-49. Please see pages 73-76 of the full guideline. We have presented separate pathways within each algorithm for people with and without a personal history of breast cancer. The algorithm has also been updated to reflect any changes made to the recommendations, and in response to comments received from stakeholders.
SH	Cancer Genetics Group	18	Full	24		Algorithm "Care and management of people in secondary care" Left hand box – 2nd paragraph "Relative with bilateral breast cancer and" Remove the "and" from the heading. There need to be separate referral criteria for women with and without breast cancer as the threshold for referral on the basis of family history is lower if that given individual has a diagnosis of breast cancer.	Thank you for your comment. This has now been updated and replaced by a box which summarises the referral criteria to a specialist genetics clinic. We have now simplified the algorithms and removed any duplication.

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						We strongly suggest separate algorithms for management in secondary care for women with a personal history of breast cancer and women without a personal history of breast cancer.	We have presented separate pathways within each algorithm for people with and without a personal history of breast cancer. The algorithm has also been updated to reflect any changes made to the recommendations, and in response to comments received from stakeholders.
SH	Cancer Genetics Group	19	Full	25		Algorithm "Care and management of people in tertiary care" The boxes on the left hand side of the algorithm are free-floating and difficult to know where they are supposed to be or the utility of them. There is no obvious connection between testing within 4 weeks of diagnosis and risk reducing surgery so this seems like a strange place to put the box. Middle box - last bullet point "consider genetic testing…..affected 1st degree relative with carrier probablility of 5-10%...Manchester Score 14-16." Should read "probability of 10-20% Manchester score 15-17) Third box on right middle bullet point "offer genetic testing to a person affected…..Manchester score of 17 " Should read Manchester score of 15 Third box on right Last bullet point " consider genetic testing….Manchester Score of 14-16" Should read "Manchester Score of 12-15"	Thank you for your comment. We agree and have simplified each algorithm to ensure all boxes are now appropriately connected, including genetic testing and risk reducing surgery. We have removed reference to the Manchester Score from the guideline as it is one of several methods of providing an estimate of probability of finding a mutation, and therefore no does warrant being given special attention. The model was based on a percentage threshold which we have retained for consistency. All references to the Manchester score have also been removed from the algorithms.
SH	Cancer National Specialist Advisory Group	1	Full	General		Based on current criteria young women with triple negative breast cancer, who have a high probability	Thank you for your comment. We hope the recommendation in the

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						of carrying mutations even in the absence of family history, cannot be referred to genetics. If they are referred they are not offered BRCA testing.	guideline will lead to a change to practice.
SH	Central Manchester University Hospital NHS Foundation Trust	1	Full	general		This proforma is difficult as there are no line numbers on the NICE version but only numbered paragraphs. I have used these for comments on the NICE version. The recommendations in the full version also do not have line numbers. I have therefore only used page numbers and have correlated the comments in both the NICE and full version.	Thank you for your comments. We will pass your concerns regarding the proforma to the Centre for Clinical Practice team at NICE.
SH	Central Manchester University Hospital NHS Foundation Trust	2	Full	general		Overall these guidelines are welcomed and are of use to the cancer genetics community, in particular with regard to those women who have a personal history of breast cancer. Previously the guidelines excluded this category. The general category of "consider" is felt to be unhelpful and is likely to lead to inequity of service across the country. Each service will need to decide whether to act on the "consider" categories, which will be influenced by local economic issues. For regional genetic services, the workload will be considerably increased if all "consider" categories are acted upon and this may actually be in conflict with referral criteria which are due to be audited against by the National Commissioning Board as part of the CQUINs scheme 2013/2014. **We strongly suggest the removal of the "consider" category from the guidelines**	Thank you 'Offer' is appropriate wording for a recommendation where the GDG is confident that, for the vast majority of people, the recommendation will do more good than harm. 'Consider' is the appropriate wording for a recommendation where the benefit is less certain and where a discussion about risks and benefits is required. Inevitably this may result in inconsistencies of practice that will reflect patient choice.
SH	Central Manchester University Hospital NHS Foundation Trust	3	full NICE	85 1.5.8		"offer genetic testing in tertiary care" "consider genetic testing in tertiary care" Tertiary care needs clarifying – if all genetic testing is to be undertaken within the Regional Genetic	Thank you for your comment. We have amended these recommendations for simplicity, and changed the term 'tertiary care' to 'specialist genetic clinics'.

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				1.5.9		Services, changing the cut off for genetic testing will substantially increase the workload into these services and potentially conflict with national referral guidelines for only high risk individuals to be seen in the Regional Genetic Services. This may cause a conflict with the National Commissioning Board's commissioning of medical genetics. If tertiary care is to include oncology/surgical services, recommendations about the information given to women need to be more explicit and funding streams for genetic testing within these specialised services need to be established. There also needs to be guidance to these services regarding confirmation of diagnosis prior to testing. Add in the Manchester Score – 12-15 (for probability of 5-10%)	This is also an implementation issue and will be highlighted to the Implementation Team at NICE We have removed reference to the Manchester Score from the guideline as it is one of several methods of providing an estimate of probability of finding a mutation, and therefore no does warrant being given special attention. The model was based on a percentage threshold which we have retained for consistency.
SH	Central Manchester University Hospital NHS Foundation Trust	4	full NICE	85 1.5.11		10-20% probability equates to Manchester Score 15-17	Thank you for your comment. We have removed reference to the Manchester Score from the guideline as it is one of several methods of providing an estimate of probability of finding a mutation, and therefore no does warrant being given special attention. The model was based on a percentage threshold which we have retained for consistency.
SH	Central Manchester University Hospital NHS Foundation Trust	5	Full NICE	85 1.5.13		Add in Manchester score of 12-15 for 5-10% probability	We have removed reference to the Manchester Score from the guideline as it is one of several methods of providing an estimate of probability of finding a mutation, and therefore no does warrant being given special attention.

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							The model was based on a percentage threshold which we have retained for consistency.
SH	Central Manchester University Hospital NHS Foundation Trust	6	full NICE	85 1.5.14		"Clinical genetic laboratories should record gene variants of uncertain significance, periodically review for evidence of causality and ensure that families are contacted as appropriate" It is not the responsibility of clinical laboratories to contact families with genetic testing results. This is the responsibility of the clinicians requesting testing. Clinicians should, when reviewing individuals, undertake an assessment of the variant and if necessary discuss with laboratory colleagues before taking a clinical decision as to whether to inform the family of any potential change in status of the variant. The guidance is open-ended and open to wide interpretation. For example, the frequency of review is unclear, should it be every 1, 2 or 5 years? Local policies may be open to challenge without more concrete guidance. It is also unclear at to which category change should be notified as laboratories use a system of categories that are subjective and require professional judgment in their application. For example, would contacting families only apply where a variant is reclassified from any other category to 'definitely pathogenic'. What if a variant is reclassified as 'probably pathogenic', potentially important information for the family but not necessarily actionable. Equally, evidence can arise that re-classifies variants as less likely to be pathogenic. Will there be a duty to also inform families when a variant changes from 'pathogenicity unknown' or 'probably pathogenic' to 'unlikely to be pathogenic'?	Thank you for your comment. We have amended and expanded this recommendation to include advice on the potential risk and benefits of genetic testing and inform families with no clear genetic diagnosis that they can request review in the specialist genetic clinic at a future date. This recommendation has been revised and it no longer recommends that clinical genetics laboratories should ensure families are contacted.

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						Classifications used by different clinical laboratories although similar are not equivalent and there will be different classifications applied by different laboratories to the same variant leading to potentially different branches of the same family being given conflicting information on the same variant. Although this is no different to the situation at reporting now, regular review will lead to more families being given conflicting information particularly as reviews between centres are unlikely to be synchronised. The process of reviewing evidence is laborious and time consuming. Currently, this process takes a Clinical Scientist 1-2 hours per variant. Within the last 18 months in Manchester, 483 samples were screened and 64 unclassified variants identified, the majority of which are rare variants unlikely to be observed more than once by the same centre. Over time, therefore the list of unclassified variants will increase (especially if offering mutation screens to larger numbers of individuals). Using current methods, reviewing the evidence for 100 UVs will take 150 hours of a clinical scientists time; a minimum of one month of a 1.0 WTE Clinical Scientist time. This statement would set a huge precedent within the laboratories. Mutation screening for BRCA1/2 is a small part of the workload for regional genetic laboratories. If regular review of UVS is required for these genes, it would be needed for all genes screened which would become untenable. The responsibility for reassessing variants and contacting the families should lie with the clinicians	

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						requesting testing. This will require education of the non-geneticists requesting genetic tests. **We strongly suggest that this statement is removed from the guidelines**.	
SH	Central Manchester University Hospital NHS Foundation Trust	7	Full NICE	91 1.5.16		"Offer people eligible for referral to a specialist genetics clinic a choice of accessing genetic testing during initial management or at any time thereafter" This seems to be contradictory to 1.5.15, which is recommending that patients are not referred to genetic testing during initial management. Further clarification is required	Thank you for your comment. However, we disagree that the recommendation is contradictory. Bullet 1 gives a precise and short time limit (within 4 weeks of diagnosis) whereas the second recommendation allows time for early referral and consideration of testing.
SH	Central Manchester University Hospital NHS Foundation Trust	8	Full NICE	116 1.6.3		"Offer annual mammographic surveillance to all women aged 40 years and over at high risk of breast cancer " It would be helpful to have an upper age limit.	Thank you for your comment. The GDG have revised the recommendations to clarify the age ranges where surveillance should be available for all the moderate and high risk groups. The GDG have acknowledged in the guideline that there was no evidence specifically relating to surveillance for women aged 70 years and over and could therefore make no specific, evidence-based recommendations. However, the GDG agreed that as these women remained at risk of breast cancer, they should still have access to surveillance. In the absence of any evidence to support enhanced surveillance, the GDG agreed that the best course of action was to

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							recommend that these women should remain in or return to the standard population screening programme.
SH	Central Manchester University Hospital NHS Foundation Trust	9	Full NICE	116 1.6.4		"Offer annual mammographic surveillance to women aged 30-39 years at moderate or high risk of breast cancer only as part of an approved research study" This is different from the previous guidelines which also allowed screening as part of an approved and audited system. Many women who are now in that audited system may need to be removed from screening. The only currently available study is due to stop recruiting in June 2013. **We suggest continuing with the previous guidelines**	Thank you for your comment. We disagree. We have revised this recommendation to now say 'Do not offer mammographic surveillance to women aged 30 - 39 years at moderate risk of breast cancer.
SH	Central Manchester University Hospital NHS Foundation Trust	10	Full NICE	116 1.6.9		"offer annual MRI surveillance to all women……aged 30-39 years who have not had a genetic test but are at greater than 30% probability of being a *BRCA1* carrier." This revision to the guidelines have removed the agreement for women at a 10 year >8% aged 30-39 years and at a 10 year >20% risk (12% with dense breasts) aged 40-49 years for MRI surveillance. This has particular impact on those women at 50% risk of inheriting a *BRCA2* mutation in a high penetrance family. By only allowing MRI surveillance to mutation carriers, this policy forces women into genetic testing. This is in direct opposition to non-directive genetic counselling which does not force a patient into testing when they may be psychologically unready to cope with results. **We strongly suggest that the original statement**	Thank you for your comment. This recommendation remains unchanged from the 2006 guideline, and there was no new evidence to support a change. This category was included because of a suggestion that women should be encouraged to undertake genetic testing in order to qualify for MRI surveillance. The number of women in this category will be very small.

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						on risk equivalence is retained in the guidelines.	
SH	Central Manchester University Hospital NHS Foundation Trust	11	Full	118 (table 7.5)		"Group 3 Untested but at greater than 30% BRCA1 carrier probability" Is this greater than 30% probability in a completely untested family or in untested woman in a known mutation family? Please clarify. Comments as for 1.6.9 also apply here	Thank you for your comment. The recommendation covers both populations.
SH	Central Manchester University Hospital NHS Foundation Trust	12	Full NICE	137 1.6.12		"Offer annual MRI surveillance to all women aged 30-39 years with a personal history of breast cancer who are at high risk of contralateral breast cancer or have a *BRCA1* or *BRCA2* mutation" Define high risk	Thank you for your comment. We define 'high risk' in chapter 2 of the full guideline.
SH	Central Manchester University Hospital NHS Foundation Trust	13	Full NICE	137 1.6.13		''Offer annual mammographic surveillance to all women age 50-69 years with a personal history of breast cancer who are at high risk of contralateral breast cancer or have a BRCA1/2 mutation '' The age at which mammography screening commences and ends surely should be the same for women with and without a personal history of breast cancer if they have a BRCA1/2 mutation	Thank you for your comment. We have amended these recommendations for consistency
SH	Central Manchester University Hospital NHS Foundation Trust	14	Full NICE	164 1.7.20		"Healthcare professionals within a specialist genetics clinic should discuss and give written information on the absolute risks and benefits (including side effects of drugs and the extent of the risk reduction) of all options for preventative treatment to women at high risk for breast cancer" Many women, referred to regional genetic services, are counselled about their breast cancer risk by genetic counsellors. Genetic counsellors often have a science degree or nursing background and have not had specific training regarding pharmacology. It	Thank you for your comment. This is an implementation issue and will be highlighted to the Implementation Team at NICE.

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						is therefore unreasonable to expect them to discuss risk and benefits of the use of (currently) unlicensed drugs. **We suggest that the statement should be modified to state that discussions around prevention should be available within a service.**	
SH	Central Manchester University Hospital NHS Foundation Trust	15	Full NICE	164 1.7.21 1.7.22		"Offer tamoxifen for 5 years to pre-menopausal women at high risk of breast cancer unless they have a past history of thromboembolic disease or endometrial cancer" "Offer tamoxifen or raloxifene for 5 years to post menopausal women ……. or endometrial cancer" There needs to be an age range stated here. Tamoxifen should not be offered to young women in their 20s. There needs to be clear guidance on who is expected to prescribe this drug. It is felt that it would be inappropriate for this to be undertaken within the regional genetics services (many individuals are not seen by a doctor) as the workload increase would be large. The inevitable queries regarding compliance, side-effects etc need to be handled via the GP and a national information leaflet (possibly produced by NICE) is needed. This also raises the question of whether a risk assessment needs to be undertaken following prescription of tamoxifen and whether some women would then fall below the threshold for annual surveillance.	Thank you for your comment. The GDG agreed not to set a minimum age limit for accessing tamoxifen or raloxifene, as they did not want to prevent young women from having access to preventative treatment as there may be some who wish to discuss options other than risk reducing surgery. This is an implementation issue and will be highlighted to the Implementation Team at NICE Chemoprevention is attempting to reduce risk but it impossible to measure any reduction on an individual basis.
SH	Central Manchester University Hospital NHS Foundation Trust	16	Full NICE	164 1.7.25 1.7.26		As 1.7.21	Thank you for your comment. The GDG agreed not to set a minimum age limit for accessing tamoxifen or raloxifene, as they did not want to prevent young women from

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							having access to preventative treatment as there may be some who wish to discuss options other than risk reducing surgery. This is an implementation issue and will be highlighted to the Implementation Team at NICE Chemoprevention is attempting to reduce risk but it impossible to measure any reduction on an individual basis.
SH	Central Manchester University Hospital NHS Foundation Trust	17	Full	23		Algorithm "Care and management of people in primary care with a personal history of breast cancer" 6th central box – bullet point 2 "Referral to tertiary care for individual with triple negative breast cancer or medullary breast cancer before 50". This is in contradiction to 1.4.5 (NICE) which suggests referral if triple negative tumour diagnosed under 40 years. This algorithm suggests direct referral to the tertiary services if any of the criteria are filled. It should be the same as the care for women without a personal history. **We suggest that the algorithm is altered to suggest that if the criteria are filled, advice is sought from the tertiary centre.**	Thank you for bringing this to our attention. This was an error in the algorithm which we have now corrected. The recommendations that cover this topic clearly state a triple negative breast cancer under the age of 40 years, as there is no strong evidence for sporadic TNT at aged 40-49. Please see page 73-76 of the full guideline. We have presented separate pathways within each algorithm for people with and without a personal history of breast cancer. The algorithm has also been updated to reflect any changes made to the recommendations, and in response to comments received from stakeholders.
SH	Central Manchester University Hospital NHS Foundation Trust	18	Full	24		Algorithm "Care and management of people in secondary care"	Thank you for your comment.

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						Left hand box – 2nd paragraph "Relative with bilateral breast cancer and" Remove the "and" from the heading. There need to be separate referral criteria for women with and without breast cancer as the threshold for referral on the basis of family history is lower if that given individual has a diagnosis of breast cancer. **We strongly suggest separate algorithms for management in secondary care for women with a personal history of breast cancer and women without a personal history of breast cancer.**	This has now been updated and replaced by a box which summarises the referral criteria to a specialist genetics clinic. We have now simplified the algorithms and removed any duplication. We have presented separate pathways within each algorithm for people with and without a personal history of breast cancer. The algorithm has also been updated to reflect any changes made to the recommendations, and in response to comments received from stakeholders.
SH	Central Manchester University Hospital NHS Foundation Trust	19	Full	25		Algorithm "Care and management of people in tertiary care" The boxes on the left hand side of the algorithm are free-floating and difficult to know where they are supposed to be or the utility of them. There is no obvious connection between testing within 4 weeks of diagnosis and risk reducing surgery so this seems like a strange place to put the box. Middle box - last bullet point "consider genetic testing…..affected 1st degree relative with carrier probability of 5-10%...Manchester Score 14-16." Should read "probability of 10-20% Manchester score 15-17) Third box on right middle bullet point "offer genetic testing to a person	Thank you for your comment. We agree and have simplified each algorithm to ensure all boxes are now appropriately connected, including genetic testing and risk reducing surgery. We have removed reference to the Manchester Score from the guideline as it is one of several methods of providing an estimate of probability of finding a mutation, and therefore no does warrant being given special attention. The model was based on a percentage

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						affected…..Manchester score of 17 " Should read Manchester score of 15 Third box on right Last bullet point " consider genetic testing….Manchester Score of 14-16" Should read "Manchester Score of 12-15"	threshold which we have retained for consistency. All references to the Manchester score have also been removed from the algorithms.
SH	Department of Health	1	Full			I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you.
SH	Eli Lilly and Company Limited and Daiichi Sankyo Europe GmbH	1	Full	164		Eli Lilly and Company Limited transferred the EU licence and certain intellectual property rights for Evista (raloxifene) to Daiichi Sankyo Europe GmbH in the EU in August 2008. Lilly remains the Marketing Authorisation Holder of Optruma (raloxifene) in the EU. Evista and Optruma are 2 identical licences for raloxifene containing product in the EU. Lilly remains the Marketing Authorisation Holder of Evista in most non-EU countries, including the US.	Thank you for this information.
SH	Eli Lilly and Company Limited and Daiichi Sankyo Europe GmbH	2	Full	164		Evista/Optruma is indicated for the treatment and prevention of osteoporosis in postmenopausal women. Evista/Optruma does not have marketing authorisation in the EU for the indication of reducing breast cancer risk.	Thank you. We have amended the background text to reflect this.
SH	Eli Lilly and Company Limited and Daiichi Sankyo Europe GmbH	3	Full	155	29-30	The document states that tamoxifen and raloxifene were developed primarily for use as adjuvant treatments for hormone receptor positive breast cancer, however, raloxifene was primarily developed for the prevention and treatment of postmenopausal osteoporosis.	Thank you for clarifying this. We have deleted the text 'developed primarily for use as adjuvant treatments for hormone receptor positive breast cancer'.
SH	Eli Lilly and Company Limited and Daiichi Sankyo Europe GmbH	4	Full	155	40	Similar to the comment above addressing the adjuvant treatment, Raloxifene has not been developed for use in the adjuvant setting (i.e. treatment of patients with breast cancer).	Thank you for pointing out this error in the background text. We have deleted this sentence.
SH	Eli Lilly and Company	5	Full	155	40-41	In the EU raloxifene is approved for the prevention	Thank you for pointing out this

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	Limited and Daiichi Sankyo Europe GmbH					and treatment of postmenopausal osteoporosis and therefore the statement that raloxifene "can increase the risk of osteoporosis and bone fractures" is incorrect. Indeed, the EU indication is "Evista is indicated for the treatment and prevention of osteoporosis in postmenopausal women. A significant reduction in the incidence of vertebral, but not hip fractures has been demonstrated."	error in the background text. It has been corrected.
SH	Eli Lilly and Company Limited and Daiichi Sankyo Europe GmbH	6	Full	155	41-42	As it pertains to the line that raloxifene "can sometimes cause intolerable muscle and joint aches and pains," this is not consistent with The EU Summary of Product Characteristics (last revision approved on 30 Aug 12) which indicates that the most significant adverse event is venous thrombotic events (blood clots) and the most common adverse events are vasodilation (hot flushes), flu symptoms, gastrointestinal symptoms* and increased blood pressure*. *Based on postmarketing experience	We have deleted this sentence from the background text to reflect these concerns.
SH	Eli Lilly and Company Limited and Daiichi Sankyo Europe GmbH	7	Full	159	Table 8.2	The effect of raloxifene in reducing the risk of breast cancer has been studied in postmenopausal women at increased risk for invasive breast cancer (STAR trial) postmenopausal women with osteoporosis (MORE/CORE), and postmenopausal women at risk for cardiovascular events (RUTH trial). The 2009 review by Nelson analyzes results from these trials. Patients with a family history of cancer could have participated in the trial but the trials were not designed to assess the effect of treatment in women with a family history ovarian or related prostate/ cancer and therefore the title appears incorrect. The patient populations in these studies were women at increased risk for invasive breast cancer using criteria that include, but were not limited to, family history. This comment applies to the related tables in this section.	Thank you for your comment. The clinical question for the topic was designed so as not to exclude women/men with related cancers such as ovarian or prostate. It was acknowledged by the GDG that the evidence would likely not be reported in this manner and that trials would not recruit with those specific criteria however it was felt that should there be evidence available which specifically addressed risks associated with related cancers, this should be included. The table title merely reflects the clinical question for the topic as is

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							this is the standard NICE protocol for labelling GRADE tables in guidelines
SH	Eli Lilly and Company Limited and Daiichi Sankyo Europe GmbH	8	Full	159	Table 8.2	The third study listed in the table*:* *Cataracts/Cataract surgery*, needs the reference date corrected from 2006 to 2009.	Thank you for bringing this to our attention, this has been amended.
SH	Eli Lilly and Company Limited and Daiichi Sankyo Europe GmbH	9	Full	165	2-3	In 2010 meta-analysis of the large placebo-controlled trials (MORE/CORE and RUTH) raloxifene was shown to modestly but significantly reduce all-cause mortality (p value = 0.05). Grady D. et al The American Journal of Medicine (2010) 123, 469.e1-469.e7	Thank you for your comment. This study did not come up in any of our searches. From looking at the abstract however, it would appear that this study is not relevant as it is not looking at mortality from breast cancer which was the outcome of interest for the topic.
SH	Genetic Alliance UK	1	Full	85 6 (KPI)	19	The wording in this section is very confusing. A number of points are being made in a single sentence that could be made in a much clearer fashion. We suggest bullet points to lay out the logical steps of this section. It is not clear to whom the "their" in this sentence refers.	Thank you for your comment. We have amended these recommendations and included appropriate sub-headings for simplicity.
SH	Genetic Alliance UK	2	Full	85 6(KPI)	24	As with the previous point, the wording here is very confusing. Given that these two points are made in parallel, the different approach in making each statement is additionally confusing. It should be clear at a glance: • Who is in the clinic • Whether they are affected or unaffected • Who is being offered testing • What is the threshold for testing Again we suggest bullets to lay out the logical steps.	Thank you for your comment. We have amended these recommendations and included appropriate sub-headings for simplicity.
SH	Genetic Alliance UK	3	Full	43		Research in different ethnic groups is welcomed but the likely impact will be several years away. Current	Thank you for your comment. It is hoped that the guideline will help

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				8 (KRR)	4	under-representation in cancer genetics services for minority ethnic patients is not being addressed.	increase representation for these patients.
SH	Genetic Alliance UK	4	Full	26		Section 1 reports on proactive approaches to tackling inherited breast cancer at the GP surgery at two points. Our findings from the study 'Access to assessment of Familial Cancer by people from minority ethnic backgrounds' highlight the particular value of a proactive approach to members of minority ethnic communities for whom discussion of this issue may be particularly difficult. Additionally the findings of Harris et al (2011) "showed that there are strong views against the current purely reactive (not actively seeking women with a family history of breast cancer) approach to familial breast cancer amongst GP's and surgeons". These are two points in favour of promoting a proactive approach. We can find no evidence quoted here against such an approach. Given the evidence in favour we strongly believe this clinical guideline should make the value of such an approach clear, and promote and facilitate proactive identification of at risk individuals and families by GPs.	Thank you for your comments. The promotion of proactive practice amongst GP's in identifying high risk patients and families based on the findings inCRisC study and 'Access to assessment of Family Cancer by people from minority ethnic backgrounds' study was not included within this guideline topic area. Therefore the GDG are unable to make any recommendations on this particular issue.
SH	Independent Cancer Patients Voice (ICPV)	1	Full	85 6(KPI)	 19	Good to see this laid down – family members should be offered this as a standard and not feel they have to ask	Thank you for your comment.
SH	Independent Cancer Patients Voice (ICPV)	2	Full	116-117 6 (KPI)	 30	Why has 40 been chosen and not 30 years of age? It is 30 years of age for those with a BRACA1 or BRACA2 mutation or someone who is part of an approved research study. We would have thought that 40 years is too old for someone at a high risk.	Thank you for your comment. We have revised these recommendations. to now say 'Consider annual mammographic surveillance for women: • aged 30-39 years at high risk of breast cancer but with a

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							30% or lower probability of a BRCA or TP53 mutation • aged 30-39 years with a greater than 30% probability of being a BRCA carrier • aged 30-39 years with a known BRCA1 or BRCA2 mutation'
SH	Independent Cancer Patients Voice (ICPV)	3	Full	116-117 6 (KPI)	 36	Good to see annual MRI for this sector – already used by many units, but not standard.	Thank you for your comment.
SH	Independent Cancer Patients Voice (ICPV)	4	Full	116-117 6 (KPI)	 33	Why stop at 50. Are they not still at moderate risk until after the menopause, which may be much later than 50 for some women. Could annual screening be recommended at least until the menopause for moderate risk women?	Thank you for your comment. There is a recommendation to say 'consider annual mammography for women aged 50-59 years at moderate risk and offer mammography as part of the population screening programme for women aged 60-69 years & 710+ at moderate risk of breast cancer' (see full guideline page 135- 138).
SH	Independent Cancer Patients Voice (ICPV)	5	Full	164 7 (KPI)	 5	We agree very strongly that tamoxifen/raloxifene should be offered as a potential chemopreventive for high risk women. There is clear evidence for this and it has been available to women in the US for some years. I know that its use in the US is low – probably due to possible effects to fertility – but that does not mean it should be denied to women. What is needed is good information on the pros and cons for taking this and **let the woman decide**. It would be good to also recommend research to	Thank you for your comments. We are confident that this recommendation does allow women to make an appropriate choice. The GDG acknowledged this an

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						compare psychosocial outcomes and clinical outcomes for those who do and do not choose to take 5 years of tamoxifen/raloxifene, given the side-effects particularly on pre-menopausal women.	important issue but did not identify this as a priority for research.
SH	Independent Cancer Patients Voice (ICPV)	6	Full 9 (KRR)	166	1	This research has to be done	Thank you for your support.
SH	Independent Cancer Patients Voice (ICPV)	7	Full 9 (KRR)	181	15	Very good to see that psychosocial research is highlighted	Thank you.
SH	Independent Cancer Patients Voice (ICPV)	8	Full NICE	180 42	1.7.54	good to see that genetic and psychological counselling is now going to be offered before risk reducing surgery	Thank you for your comment.
SH	Independent Cancer Patients Voice (ICPV)	9	Full NICE	184 44	1.7.63	Limited life expectancy is not defined and should be	Thank you for your comment. The GDG felt that they were unable to define this further and clinical judgement should be used on a case by case basis.
SH	Independent Cancer Patients Voice (ICPV)	10	Full	General		This looks very big improvement and we like the emphasis on real discussion with the people affected re pros and cons in testing and ongoing care. There is much more clarity about criteria for testing and the need for this to be done by those with appropriate expertise and in a centre able to offer time, counselling etc It is good to have the clear recommendation re use of Tamoxifen and Raloxifene for prevention and for research to be carried out re aromatase v Tamoxifen to enable women to have more choice.	Thank you for your comment. We agree. Thank you. Thank you. We agree.

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						Also clear recommendations re when MRI, Ultrasound and Mammography should be used and the need for any reconstructive surgery to be done by specialist surgeons.	Thank you.
SH	Independent Cancer Patients Voice (ICPV)	11	Full	General		Very good to see a wide range of research topics listed – all are relevant and would seem to fit gaps in knowledge. These should be encouraged.	Thank you for your comment.
SH	Independent Cancer Patients Voice (ICPV)	12	Full	164		When ICPV first heard that tamoxifen could not be used as a chemopreventive in the UK we were shocked. The original patent holder did not want to proceed and the regulatory authorities would not move without the original patent holder. We strongly felt that the system needs to be looked at as there are many other drugs that are or are almost out of patent and may have uses beyond their original registration. It is to be applauded that NICE is taking up this position with tamoxifen.	Thank you for your comment.
SH	Institute of Cancer Research	1	Full	94	7	We welcomed and discussion regarding the timing of BRCA testing. We are personally undertaking research directed towards this as recommended on page 8 line 19. However, we believe the second recommendation 'offer eligible for referral to a specialist clinic a choice of accessing genetic testing during initial management or anytime thereafter' is sufficient. We would prefer for the first recommendation –'Do not offer fast track testing except as part of a clinical trial' to be removed or toned down. For example instead of 'Do not…' it could be 'We recommend that if fast track testing is offered it should be as part of a clinical trial'. As currently written it contradicts the second recommendation, it is overly prescriptive, there are no clinical trials in which patients can participate, and it fails to recognise the situations in which women with breast cancer are already well versed in the issues and want to have testing (an	Thank you for your comment. The guideline makes it clear that genetic testing at any point in time including during the course of primary breast cancer treatment can be offered to people with breast cancer who fulfil the referral criteria. There is no evidence of any benefit of rapid genetic testing for people newly diagnosed with breast cancer, and therefore a research recommendation was made in order to address this gap.

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						increasing scenario). Testing time is decreasing rapidly and patient awareness is increasing rapidly. Thus there is a danger that this recommendation will become rapidly out-of-date, particularly the term 'fast track'. There is also a concern that it will encourage patients to access DTC testing because they cannot get NHS testing. We also felt that the discussion would benefit from recognising that most tests are negative and therefore can reduce anxiety and increase confidence in conservative surgery. Some women elect to have more substantial surgical procedures because the BRCA result is not available in time. This situation should be avoided wherever possible. Overall, we feel the needs of the individual patient and their personal cancer history is paramount. This will impact on timing of discussions and thus doctors need the flexibility to be able to address the issues of testing at the most appropriate time in the patient pathway (as per recommendation 2).	
SH	Institute of Cancer Research	2	full	62	1	We welcome the addition of triple-negative breast cancer as an eligibility criterion for BRCA testing. However, we recommend that the eligibility should be triple negative breast cancer **below age 50** years (not below 40 years). There is published evidence from UK and US that such women have a >10% chance of carrying a mutation and that testing is cost-effective. Therefore, they should be included in the recommendations. Moreover, many centres in UK are already offering testing to TN <50 years. It would be poor medicine and poorly received to reduce this access, particularly when unaffected women with lower likelihood of having a mutation are being recommended access to testing in the new guidance.	Thank you for your comment. The evidence that women under the age of 40 with no known family history of breast cancer exceed the 10% threshold is clear. However for women aged 40 -50 with no known family history, the decision on genetic testing should still be based on the probability of finding a BRCA mutation. In a women aged 40-50 with a triple negative breast cancer and any close relative with breast or ovarian cancer would easily exceed the threshold and therefore access testing.

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SH	Institute of Cancer Research	3	full	68	1	We would recommend that 'it is not sensible to test all women with breast cancer' is changed to 'it is not currently feasible to test all women with breast cancer'. As costs decrease and access to genetic testing increase it is entirely possible that it will be more 'sensible' / efficient / acceptable to test all women at some stage in the future.	Thank you for your comment. We have amended this sentence to 'it is currently impractical to test all women with breast cancer'.
SH	Institute of Cancer Research	4	full	164 7 (KPI)	 5	We request clarification regarding whether the recommendation of tamoxifen is for post-menopausal women as stated here, or premenopausal women as stated on page 26, line 3.	Thank you for your comment. This recommendation refers to post-menopausal women and is one of 10 key priority recommendations selected by the GDG using set criteria as defined in the NICE guidelines manual (2012). Unfortunately the recommendation for pre-menopausal women was not selected.
SH	Institute of Cancer Research	5	full	176	6	There was considerable concern from many at Royal Marsden Hospital regarding the recommendation that tamoxifen / raloxifene should be prescribed. This is a substantial change from previous guidance and could have substantial implications for many women (for example most will have to pay for their prescription) and the health service. We therefore request fuller information about who should be offered these drugs and how this recommendation should be implemented e.g. the optimal age at which it should be given, and the information about the risks and benefits that should be provided. Presumably, the recommendation does not include gene carriers? We are not aware of evidence	Thank you for your comment. The GDG agreed not to set a minimum age limit for accessing tamoxifen or raloxifene, as they did not want to prevent young women from having access to preventative treatment as there may be some who wish to discuss options other than risk reducing surgery. There is a clear recommendation on the giving of written information on the risk and benefits the drugs, including side effects. We have recommended that these drugs can be given to people at

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						showing benefit in that setting. There was concern about using these drugs for non-licensed uses, please could any implications for doctors/trusts be clarified.	high risk of being a gene carrier which would include BRCA gene carriers. There is high quality evidence of a benefit in reducing breast cancer incidence for both tamoxifen and raloxifene. The MHRA were invited to respond and no concerns were raised.
SH	Institute of Cancer Research	6	full	43 8 (KRR)	11	We greatly welcome the recommendation to offer testing to people with 10% likelihood of carrying a mutation and to consider testing at 5%.	Thank you. However the recommendations to consider genetic testing at 5-10% have been removed from the guideline. The GDG agreed that lowering the threshold to 5% would increase the number of patients eligible for genetic testing and potentially overload the existing service. In addition the GDG did not wish to recommend a lower threshold than most other countries worldwide who offer genetic testing.
SH	Institute of Cancer Research	7	full	88	1	We welcome recommendations regarding testing in unaffected women. However, we are concerned that the recommendations may be inconsistent with regard to unaffected and affected women, i.e. one seemingly requires a lower threshold for having a test if one is unaffected than if one is affected. Under the current guidance a woman with TN breast cancer at 42 (see above) or breast cancer at 32 or bilateral bc at 42 would not be eligible for testing whereas multiple unaffected relatives with fairly modest family history of breast cancer could be eligible. We recommend that additional criteria for affected women should be included. For	Thank you for your comments. Emphasis is on the threshold for testing which can take into account tumour pathology as well as age at onset and the wider family history. It is not possible to specify every potential scenario. Guidance from specialist genetic clinic can always be requested.

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						example women with young-onset breast cancer, and women with bilateral breast cancer, to ensure that affected women are not at risk of being disadvantaged (many will be seen in secondary care and no family history will be taken). Having a test result in an affected individual also improves the information available to relatives.	
SH	London Cancer Alliance	1	Full	116		Disagree that MRI surveillance strategy for women should not be offered over 49 years of age. Also this is at odds with NHSBSP guidance.	Although there was some evidence on MRI surveillance in individuals aged 50 and above the GDG concluded this was not sufficiently strong to increase the upper age limit.
SH	London Cancer Alliance	2	Full	General		Family or personal history of polyposis coli and Peutz Jeghers syndrome has not been included.	Thank you for your comments. We have added these groups to the surveillance recommendations. This guideline refers to the care of people with a family history of breast cancer. There is also no evidence base for screening in these conditions other than based on risk. Risk based screening is already included in this guideline.
SH	London Cancer Integrated Cancer System	1	Full	General		Overall these guidelines are helpful, and clarify screening programmes for women at familial risk. We are pleased to see they now include women who have a personal history of breast cancer. We support the lowering of the threshold for offering BRCA testing to affected women, and unaffected women in high risk families where no affected relative is available for testing. Annual mammography for over 50s at moderate	Thank you. We agree. These are also key

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						risk, and tamoxifen for moderate risk women are the areas in these guidelines that have the greatest implications for service provision in secondary care. The NBSS have issued draft guidelines with screening recommendations that differ from those recommended by NICE, particularly with regard to cut off for offering mammograms to women in the moderate risk group. We think it is important that there is agreement between NICE and NBSS otherwise this may lead to confusion for both providers and commissioners, and inequity of provision. The general category of "consider" is likely to lead to inequity of access to genetic testing and chemoprevention across the country. We feel that this should be removed. With regard to genetic testing, if offered to unaffected women in the 'consider' group, this would be contrary to the advice from the National Commissioning Board (as part of the CQUINs scheme 2013/2014) for genetics services not to see moderate risk unaffected women. **We think the "consider" category is unhelpful and suggest it is removed from the guidelines.**	issues for implementation and will be highlighted to the Implementation Team at NICE. This guideline was produced using the best available evidence of clinical and cost effectiveness. The GDG, NCC-C and NICE will be working closely with the NHSBSP to consider whether national screening protocols for higher risk women should be updated to reflect the updated NICE guideline. 'Offer' is appropriate wording for a recommendation where the GDG is confident that, for the vast majority of people, the recommendation will do more good than harm. 'Consider' is the appropriate wording for a recommendation where the benefit is less certain and where a discussion about risks and benefits is required. Inevitably this may result in inconsistencies of practice that will reflect patient choice.
SH	London Cancer Integrated Cancer System	2	Full NICE	42 15	1.1.9	Manchester score does not give 10 year risk, so to do a 'proper' assessment will require either Manchester Score plus one of the other models, or one of the other models alone. Also, noted that Tyrer-Cuzick is not mentioned (though not excluded). It is widely used by secondary care services. BOADICEA is widely used in genetics but	Thank you for your comment. The Manchester score is only used for mutation probability assessment, not cancer risk (either lifetime or 10-year). Tyrer-Cuzick was considered as

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						is time consuming, the interface is not designed for use in a busy clinic setting, and would need more staffing to implement routinely in secondary care. We ask NICE to consider service implementation here.	part of the evidence review (it is also known as IBIS). We note it is routinely used for cancer risk assessment in secondary care but not for mutation probability estimation. We did not specifically recommend extending its use in secondary care - we only recommended using these tools where they are currently available because of the training implications. This is also an implementation issue and will be highlighted to the Implementation Team at NICE
SH	London Cancer Integrated Cancer System	3	Full NICE	85 28	 1.5.9	We presume that tertiary care means Regional Genetic Services but this should be made explicit. Changing the cut off for genetic testing to 5-10% will conflict with guidelines from the National Commissioning Board for only high risk individuals to be seen in the Regional Genetic Services. Funding for additional genetic testing would need to be established, as well as the clinicians to see and counsel additional families. If tertiary care is to include oncology/surgical services, this should be stated; it would be different from the current model of providing genetic testing and would have considerable training and service implications. Again we ask NICE to consider service provision here.	Thank you for your comment. We have replaced 'tertiary care' with 'specialist genetic clinic'. Thank you for raising these important issues. Based on your comments and those received from other stakeholders we have decided to delete the recommendations to consider genetic testing at a threshold between 5-10% and these have been removed from the guideline. The GDG agreed that lowering the threshold to 5% would increase the number of patients eligible for genetic testing and potentially overload the existing service. In addition the GDG did not wish to recommend a lower threshold than

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							most other countries worldwide who offer genetic testing.
SH	London Cancer Integrated Cancer System	4	Full NICE	85 28	 1.5.10	We support this, although 'unavailable for testing' is open to interpretation and needs to be defined. Will put greater pressure on genetics services such as our own, for example, where there are large migrant populations.	Thank you for your comment.
SH	London Cancer Integrated Cancer System	5	Full NICE	85 28	 1.5.11	See 1.5.9. This group includes moderate risk women	Thank you for your comment. Yes we agree. This is based on the outcome of the economic model.
SH	London Cancer Integrated Cancer System	6	Full NICE	85 29	 1.5.13	See 1.5.9	Thank you for your comment. We have replaced 'tertiary care' with 'specialist genetic clinic'. This is also an implementation issue and will be highlighted to the Implementation Team at NICE Our recommendations are based on evidence of both clinical and cost effectiveness.
SH	London Cancer Integrated Cancer System	7	Full NICE	85 29	 1.5.14	**Clinical genetics laboratories should record gene variants of uncertain significance, periodically review for evidence of causality and ensure that families are contacted as appropriate. [new 2013]** Implementing this in practice will be difficult and the workload involved in reviewing evidence will be substantial. The frequency of review is not specified, nor the indications for notifying families. There is no internationally accepted system used to classify variants. If different classifications are applied by different laboratories to the same variant this might lead to different branches of the same family being given conflicting information. Although	Thank you for your comment. We have amended and expanded this recommendation to include advice on the potential risk and benefits of genetic testing and inform families with no clear genetic diagnosis that they can request review in the specialist genetic clinic at a future date.

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						this is no different to the current situation, regular review will lead to more families being given conflicting information. The process of reviewing evidence needs to be carried out for each individual variant is time-consuming. The majority are rare and the list of variants that is proposed to be reviewed will grow year on year. This is a substantial commitment for a diagnostic laboratory and does not consider genes other than BRCA1 and 2. The anticipated demand could not be met with current staffing levels without impacting on other areas of work. There is also an impact for Clinical Genetics in communicating the information to anxious families. It is not the responsibility of clinical laboratories to contact families with genetic testing results. This is the responsibility of the clinicians requesting testing. Clinicians should, when reviewing individuals, undertake an assessment of the variant and if necessary discuss with laboratory colleagues before taking a clinical decision as to whether to inform the family of any potential change in status of the variant. **We think this statement should be removed from the guideline as currently it is not practicable to implement this within the NHS**.	
SH	London Cancer Integrated Cancer System	8	Full NICE	91 29	1.5.15	**"**do not offer fast track genetic testing……except as part of a clinical trial" We broadly support this, but there are a handful of clinical situations in which fast track testing may impact upon clinical management of an individual undergoing treatment for breast/ovarian cancer. For example, the decision regarding surgical treatment of DCIS may be altered with knowledge of BRCA1/2 status. **We suggest that this statement be altered to allow testing on a case-by-case basis following discussion with the local consultant cancer geneticist**	Thank you for your comment. The guideline makes it clear that genetic testing at any point in time including during the course of primary breast cancer treatment can be offered to people with breast cancer who fulfil the referral criteria. There is no evidence of any benefit of rapid genetic testing for people newly diagnosed with

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							breast cancer, and therefore a research recommendation was made in order to address this gap. Additionally the GDG could not support a recommendation to offer rapid testing on a widespread basis as the systems are not in place to support this. Whilst it was acknowledged that identification of a BRCA1/2 mutation could have significant impact on the choice of primary treatment, a high proportion of triple negative breast cancers now receive neo-adjuvant chemotherapy which allows much more time for test information to be properly assimilated.
SH	London Cancer Integrated Cancer System	9	Full NICE	116-117 30	1.6.3	"Offer annual mammographic surveillance to all women aged 40 years and over at high risk of breast cancer " Need to have an upper age limit.	Thank you for your comment. The GDG have revised the recommendations to clarify the age ranges where surveillance should be available for all the moderate and high risk groups. The GDG have acknowledged in the guideline that there was no evidence specifically relating to surveillance for women aged 70 years and over and could therefore make no specific, evidence-based recommendations. However, the GDG agreed that as these women remained at risk of breast cancer, they should still have access to surveillance. In the absence of any evidence to support enhanced

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							surveillance, the GDG agreed that the best course of action was to recommend that these women should remain in or return to the standard population screening programme.
SH	London Cancer Integrated Cancer System	10	Full NICE	116-117 30	1.6.4	"Offer annual mammographic surveillance to women aged 30-39 years at moderate or high risk of breast cancer only as part of an approved research study" This is problematic as the only currently available study is due to stop recruiting in June 2013. It is different from the previous guidelines which also allowed screening as part of an approved and audited system. Some women may need to be removed from screening if this is adopted.	Thank you for your comment. We agree. Therefore we have revised this recommendation to now say 'Do not offer mammographic surveillance to women aged 30 - 39 years at moderate risk of breast cancer. This is because the risk of breast cancer in the moderate risk group is low and there continues to be a concern of the potential harm of radiation to young breast tissue and the incidence of radiation-induced cancers. We have added additional information in the LETR paragraph.
SH	London Cancer Integrated Cancer System	11	Full NICE	116-117 31	1.6.8	Consider here could lead to inequities and there are major implications for services if all moderate risk women over 50 are screened annually. Need to have an upper age limit.	Thank you for your comment. The GDG have revised the recommendations to clarify the age ranges where surveillance should be available for all the moderate and high risk groups. The GDG have acknowledged in the guideline that there was no evidence specifically relating to surveillance for women aged 70 years and over and could therefore make no specific, evidence- based recommendations. However, the GDG agreed that as

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							these women remained at risk of breast cancer, they should still have access to surveillance. In the absence of any evidence to support enhanced surveillance, the GDG agreed that the best course of action was to recommend that these women should remain in or return to the standard population screening programme.
SH	London Cancer Integrated Cancer System	12	Full NICE	116-117 31	1.6.9	"offer annual MRI surveillance to all women……aged 30-39 years who have not had a genetic test but are at greater than 30% probability of being a *BRCA1* carrier." We are concerned that this excludes women who may be at risk of inheriting a *BRCA2* mutation. By only allowing MRI surveillance to mutation carriers, this policy forces women into predictive genetic testing for BRCA2 if they wish to access screening. Non-directive genetic counselling specifically does not encourage a patient to undergo testing when they may be psychologically unready to cope with results. We suggest that a statement on risk equivalence is retained in the guidelines.	Thank you for your comment. This recommendation has now been revised to include both BRCA1 and BRCA2 carriers as you have suggested.
SH	London Cancer Integrated Cancer System	13	Full NICE	137 33	1.6.13	''Offer annual mammographic surveillance to all women age 50-69 years with a personal history of breast cancer who are at high risk of contralateral breast cancer or have a BRCA1/2 mutation '' High risk should be defined. The age at which mammography screening commences and ends should be the same for high risk women with and without a personal history of breast cancer. See 1.6.3 and 1.6.8	Thank you for your comment. We have amended these recommendations for consistency

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SH	London Cancer Integrated Cancer System	14	Full NICE	164 38	 1.7.21 1.7.22	"Offer tamoxifen for 5 years to pre-menopausal women at high risk of breast cancer unless they have a past history of thromboembolic disease or endometrial cancer" "Offer tamoxifen or raloxifene for 5 years to post menopausal women ……. or endometrial cancer" There needs to be an age range stated here, specifically regarding when it would be appropriate to start treatment, in pre-menopausal women given in both trials the minimum age was 35 years. There also needs to be clear guidance on who is expected to prescribe this drug. Many patients in genetics services are seen by genetic counsellors who are not medically trained; in many family history clinics in secondary care they are seen by specialist nurses. Queries regarding compliance, side-effects etc, need to be handled via the GP and a national information leaflet (possibly produced by NICE) is needed. GPs may be reluctant to prescribe a drug for an unlicensed indication. Furthermore, the endpoints in the studies quoted in the full guideline were breast cancer risk reduction, not reduced all-cause mortality. The one study that looked at this (IBIS1) showed a greater mortality in the tamoxifen group.	Thank you for your comment. The GDG agreed not to set a minimum age limit for accessing tamoxifen or raloxifene, as they did not want to prevent young women from having access to preventative treatment as there may be some who wish to discuss options other than risk reducing surgery. This is an issue for implementation and will be highlighted to the Implementation Team at NICE It is important to weigh up risk and benefits for an individual before agreeing tamoxifen prevention might be appropriate and this is covered in the recommendations.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	1	Full	116-117 6 (KPI)	 30	What is meant by personal history? Does this mean that the person themselves must have had cancer.	Thank you for your comment. Yes, this does mean the person must have had cancer. We have defined this term in the glossary.

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SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	2	Full	137 6 (KPI)	 46	What is considered as high risk? The document does not provide this guidance.	Thank you for your comment. A definition of high risk is defined in chapter 2.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	3	Full	164 7 (KPI)	 7-16	Information must also be provided around the use of tamoxifen. If the risk of developing cancer is linked to the development of triple negative breast cancer provision of hormone therapy may not be of benefit the patient must be aware of this and have the full information to make an informed decision that is correct for them.	Thank you for your comment. We have added additional information to the background text. There was insufficient evidence of a specifically different effect in BRCA gene carriers. So we have amended the background section to include the ER specific risk reduction. Therefore the recommendations have not been amended as the risks should be discussed on an individual basis.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	4	Full	22	3 box in flow chart	One 1st degree relative with breast cancer before 40. Does this also include those diagnosed at the age of 40 or is it actually 39 and younger.	Thank you for your comment. This recommendation refers to people aged 39 years and younger.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	5	Full	22	5th box down in centre stream.	'Are any of the following present in the family history?...' We understand that other cancers such as pancreatic are also associated with BRCA. What about the cancer genes that are not yet identified but where there is a clear family history indicative of familial breast cancer in 1st degree relatives and such as pancreatic cancer in second degree relatives.	Thank you for your comment. We acknowledge that pancreatic cancer is associated with BCRA2 mutations but the evidence was not reviewed as it was outside the scope of the guideline.
SH	National Cancer Research Institute / Royal College of	6	Full	23	table	Be clear when referring to ages. The before age… does this also include the age stated?	Thank you for your comment. The recommendation refers to people

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	Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology						before the age the aged stated i.e. before aged 40 means up to age 39)
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	7	Full	34	489 - 51	This seems very focused on the older woman and does indicate that consideration to the younger woman has been given. A family history of breast cancer will have a greater impact on the younger woman with longer terms considerations.	Thank you for your comment. However, we disagree because the statement applies across all age groups.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	8	Full	35	table	The title of the table does not make it clear what information it is providing without reading the preceding information.	Thank you for your comment. We agree. The title has been revised to read 'Summary of breast cancer risk categories and related care settings'.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	9	Full	35	table	Primary, secondary and tertiary care needs to be clarified. Consideration also needs to be given in respect of terminology given the pending NHS reconfiguration	Thank you for your comment. However, we disagree. These settings are already well defined and understand by healthcare professionals. However we have replaced 'tertiary care' with 'specialist genetic clinic throughout the guideline. A definition for a specialist genetic clinic has also been included in the glossary. The guideline has been developed in the context of current NHS service configuration and it is difficult to take account and predict future changes to services.
SH	National Cancer Research Institute / Royal College of	10	Full	39	Grey sectio	If medical records are to be accessed for family members other than the patient in consultation, the	Thank you for your comment. Only the new and updated

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	Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology				n 6th bullet point	legitimate relationship with that 'other family member' should be considered. What about patient confidentiality? Both patients should have their own confidentiality observed. Does consent need to be obtained?	recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	11	Full	49	Grey box Recommendations	Information on risk should be given on a personal level, with regional and national comparisons to help informed decision making. For example, patients in a the same category of diagnosis with the same profile and family history the risk is ….	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	12	Full	52	Grey box	Relatives. It needs to be clear if the number of first, second or third degree relatives are specific to the paternal or maternal side of if this a can be a combination or maternal and paternal relatives.	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	13	Full	52	Grey box	Direct referral to Genetics service should be possible for those patients that have had their own diagnosis of cancer. It is not clear if the last bullet point refers only to those patients that have relatives who have had breast cancer.	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	14	Full	53	7-10	Information about all relevant cancers with a genetic link should be made available to the patient. ie in such as BRCA1 and BRCA 2 may also have an increased risk of skin cancer, pancreatic cancer etc. This may not be considered as unnecessary anxiety but will help the patient to be more aware of symptoms that would indicate they need to seek further investigations and potentially earlier interventions leading to a treatable situation rather than a terminal illness.	Thank you for your comment. We agree that families with a BRCA1 or BRCA2 gene alteration may have risks in addition to breast and ovarian cancer for which genetic counselling may be available. The statement in the guideline is meant to be more general with regard to anxiety associated with a family history and it is the role of the

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							genetic counsellor to explore these additional concerns with the individual.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	15	Full	55	Recommendations	Some of the information in this box is a repeat of a box in previous sections. This expands the document unnecessarily.	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	16	Full	61	11	It would be useful to know the associated lifetime risk for TP53, E-Cadherin and STK11	Thank you for your comment. There is a lack of information on the lifetime risks for these mutations and therefore the GDG were unable to include these in their recommendations.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	17	Full	74	18-25	This does not mention the impact of those with a family history of breast cancer but with no identified genes. ie they may have tested negative for the known mutations. A negative genetic result can lead to anxiety and uncertainty. It may not be possible for the patient to make a fully informed decision due to lack of known genetic information.	Thank you for your comment. A QALY decrement was applied for every person undergoing genetic testing irrespective of their BRCA test results to account for anxiety and uncertainty associated with genetic testing in the model cycle genetic testing took place in.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	18	Full	91	41-45	This is applauded and welcomed.	Thank you.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	19	Full	116	Bullet 5	Why refuse mammographic monitoring to TP53 carriers under the age of 50 but offer it to those over the age of 50? What other form of monitoring would be offered to those under 50?	Thank you for your comment. The recommendation is to offer MRI surveillance for all age groups. The GDG decided not to recommend mammography for TP53 carriers at any age due to

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							the increased hypothetical risk of malignancy.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	20	Full	117	Bullet 4	Seems to contradict guidance given as per above comment regarding mammography to the under 50's	The GDG decided not to recommend mammography for TP53 carriers at any age due to the increased hypothetical risk of malignancy. Therefore this recommendation is not contradictory.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	21	Full	117	Last Bullet	Will no surveillance be offered to those who have undergone bilateral mastectomy?	Thank you for your comment. We feel that having risk reducing surgery means you are no longer in the risk category for screening.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	22	Full	120	27-31	This practice difference should be amended so that the patient with the primary tumour has continued monitoring	This is background text as to why the clinical question was researched.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	23	Full	128	3-11	Identified subject for further investigation and studies to be undertaken – perhaps?	Thank you for your comment. This is introductory text to the cost effectiveness model.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	24	Full	140	Recommendation	Patient could be offered annual mammogram with no time limit. Where is theevidence that annual mammography for moderate risk women to age 70 is efficacious?	Thank you for your comment. The evidence was not reviewed for moderate risk women. However, the GDG agreed that surveillance should be consistent with the recommendations that have already been produced as part of the NICE early breast cancer guideline (CG80) and reference to

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							these has been included in the full guideline, section 7.3.1.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	25	Full	148	Recommendation	Should the woman not be offered a genetic test to assist their decision in respect to oral contraceptives?	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	26	Full	150		There is no indication of use of HRT for women with history of triple negative cancer. Guidance here would be valuable to help inform the patient.	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	27	Full	151	Recommendation	HRT guidance specific Triple negative recommendation required..	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	28	Full	156	24-47	Specific note should be made in respect of chemoprevention in respect to triple negative tumours risk. However it is welcomed that the option is available to patients for chemoprevention	Thank you for your comment. We have added additional information to the background text. There was insufficient evidence of a specifically different effect in BRCA gene carriers. So we have amended the background section to include the ER specific risk reduction. Therefore the recommendations have not been amended as the risks should be discussed on an individual basis

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SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	29	Full	164	recommendation	Risk associated with pregnancy should be highlighted in respect of hormone changes for hormone driven tumours	Thank you for your comment. The guideline recommends that women stop taking tamoxifen 2 months prior to conceiving.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	30	Full	116		A mortality benefit from family history screening is assumed even although there is little evidence for this. This is of particular concern when screening for BRCS 1 carriers where the lack of size/outcome for basal cancers is noted. Investigating the mortality benefits for screening does not but should figure in the areas recommended for further research.	Thank you for your comment. Research in this area would also be impractical. Any study undertaken would have to be a randomised controlled trial and recruitment would be extremely difficult. In order to get meaningful data you would need a very high number of participants in the trial and at least 30 years of follow up.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	31	Full	General		At times, the document appears to lack structure and flow which results in information that would help provide a basis for understanding later in the document is not present until the specifics are raised later in the document. eg first degree relatives, second degree relatives these are not clarified until page 36, however reference to close relatives are mentioned far earlier in the document. The same format for each chapter should be consistent, eg chapter 5 provides the purpose of the chapter, whereas preceding chapters are not so clear.	Thank you for your comments. Developing this guideline has presented the GDG and NCC-C with a variety of challenges. What we were asked to do was update the existing familial breast cancer guideline (CG14/14) and to incorporate a new set of recommendations on the management of people with a personal history of breast. However the GDG were not permitted to change any of the recommendations from topics in CG14/41 that were not updated. These topics were clearly presented and explained in the guideline scope. As a result there are places in the guideline that are

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							different in style and presentation compared to the updated and new sections. We have attempted to provide sufficient information in Chapter 2 to enable the reader to understand and interpret the more specific recommendations later in the document. The presentation and order of each chapter is consistent, however the depth and content does vary as we were not able to significantly alter sections we were not updating. Nevertheless the GDG has attempted to improve the structure and flow of the guideline and has tried to ensure the language, terminology and style are consistent throughout.
SH	National Cancer Research Institute / Royal College of Physicians / Association of Cancer Physicians / Joint Collegiate Council for Oncology	32	Full	General		The NCRI/RCP/ACP/JCCO is grateful for the opportunity to respond to the guideline consultation. Our submission is based on comments received from our experts in the treatment of breast cancer and patient advocates.	Thank you for your comments.
SH	NHS National Cancer Screening Programmes	1	NICE			Generally very clear and good that scope includes women at high familial risk with previous history of breast cancer.	Thank you.
SH	NHS National Cancer Screening Programmes	2	Full NICE	116-117 30	1.6.3	Is there an upper age limit for high risk >40 years to be offered annual mammography? Perhaps aged 69 as in paragraph 1.6.13.	Thank you for your comment. The GDG have revised the recommendations to clarify the age ranges where surveillance should be available for all the

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							moderate and high risk groups. The GDG have acknowledged in the guideline that there was no evidence specifically relating to surveillance for women aged 70 years and over and could therefore make no specific, evidence-based recommendations. However, the GDG agreed that as these women remained at risk of breast cancer, they should still have access to surveillance. In the absence of any evidence to support enhanced surveillance, the GDG agreed that the best course of action was to recommend that these women should remain in or return to the standard population screening programme.
SH	NHS National Cancer Screening Programmes	3	Full NICE	116-117 31	1.6.8	This recommendation is very vague and no use to clinicians – it should either be recommended or a research topic.	Thank you for your comment. The GDG felt that a research recommendation was not appropriate as annual mammographic surveillance should be considered for women aged 50-59 years at moderate risk rather than mammography as part of the population screening programme. 'Consider' is the appropriate wording for a recommendation where the benefit is less certain and where a discussion about risks and benefits is required.
SH	NHS National Cancer	4	Full	116-		The NHS Breast Screening Programme guidance	Thank you for your comment. We

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	Screening Programmes		NICE	117 31	1.6.11	for women at very high risk eligible for MRI scanning includes a comment that MRI scanning can be considered >50 years where there is a dense background pattern. Could the guidelines be consistent to avoid confusion?	agree and have amended these recommendations to say 'do not offer MRI, unless mammography has shown a dense breast pattern'.
SH	NHS National Cancer Screening Programmes	5	Full	42 6 (KPI)	7-8	Should there be an agreed list of assessment tools and techniques	Thank you for your comment. The GDG noted there were only small differences in performance between existing methods of assessing carrier probability and so they were unable to recommend one method over another. However for illustrative purposes, the GDG agreed to cite BOADICEA and the Manchester Score as examples of models in common use in the UK. The BOADICEA method is a computer-based tool whereas the Manchester Score can be calculated on paper and so provides healthcare professionals the option of either approach to calculating carrier probability. Because of the lack of evidence for this topic the GDG did not wish to prohibit healthcare professionals from using other methods with demonstrated acceptable performance should they wish to do so.
SH	NHS National Cancer Screening Programmes	6	Full	116	1	It would be helpful to be consistent with NHSCSP guidance which has been agreed by the Advisory Committee on Breast Cancer Screening http://cancerscreening.nhs.uk/breastscreen/publications/nhsbsp74.html (Publication No.74)	Thank you for your comment. The GDG developed their recommendations based on all the available evidence for the topic of 'specific surveillance needs of

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							women with a family history but with no personal history of breast cancer', following the methodology within the NICE guidance development manual which is available on the NICE website: (http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/clinical_guideline_development_methods.jsp). We acknowledge there are some inconsistencies with the NHSBSP guidance but these are discussed and explained in the linking evidence to recommendations section on page 144 of the full guideline.
SH	NHS National Cancer Screening Programmes	7	Full	116	1	As above	Thank you for your comment. The GDG developed their recommendations based on all the available evidence for the topic of 'specific surveillance needs of women with a family history but with no personal history of breast cancer', following the methodology within the NICE guidance development manual which is available on the NICE website: (http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/clinical_guideline_development_methods.jsp). We acknowledge there are some inconsistencies with the NHSBSP guidance but these are discussed

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							and explained in the linking evidence to recommendations section on page 144 of the full guideline.
SH	NHS National Cancer Screening Programmes	8	Full	116	1	As above	Thank you for your comment. The GDG developed their recommendations based on all the available evidence for the topic of 'specific surveillance needs of women with a family history but with no personal history of breast cancer', following the methodology within the NICE guidance development manual which is available on the NICE website: (http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/clinical_guideline_development_methods.jsp). We acknowledge there are some inconsistencies with the NHSBSP guidance but these are discussed and explained in the linking evidence to recommendations section on page 144 of the full guideline.
SH	NHS National Cancer Screening Programmes	9	Full	117		Should there be an agreed and accepted list of assessment methods. Not just an example of an accepted one?	Thank you for your comment. The GDG noted there were only small differences in performance between existing methods of assessing carrier probability and so they were unable to recommend one method over another. However for illustrative purposes, the GDG agreed to cite

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							BOADICEA and the Manchester Score as examples of models in common use in the UK. The BOADICEA method is a computer-based tool whereas the Manchester Score can be calculated on paper and so provides healthcare professionals the option of either approach to calculating carrier probability. Because of the lack of evidence for this topic the GDG did not wish to prohibit healthcare professionals from using other methods with demonstrated acceptable performance should they so wish to do so.
SH	NHS National Cancer Screening Programmes	10	Full	118	3	It would be helpful to be consistent with NHSCSP guidance which has been agreed by the Advisory Committee on Breast Cancer Screening http://cancerscreening.nhs.uk/breastscreen/publications/nhsbsp74.html (Publication No.74)	Thank you for your comment. The GDG developed their recommendations based on all the available evidence for the topic of 'specific surveillance needs of women with a family history but with no personal history of breast cancer', following the methodology within the NICE guidance development manual which is available on the NICE website: (http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/clinical_guideline_development_methods.jsp). We acknowledge there are some inconsistencies with the NHSBSP guidance but these are discussed

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							and explained in the linking evidence to recommendations section on page 144 of the full guideline.
SH	NHS National Cancer Screening Programmes	11	Full	118	14-17	As above	Thank you for your comment. The GDG developed their recommendations based on all the available evidence for the topic of 'specific surveillance needs of women with a family history but with no personal history of breast cancer', following the methodology within the NICE guidance development manual which is available on the NICE website: (http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/clinical_guideline_development_methods.jsp). We acknowledge there are some inconsistencies with the NHSBSP guidance but these are discussed and explained in the linking evidence to recommendations section on page 144 of the full guideline.
SH	NHS National Cancer Screening Programmes	12	Full	120	27-31	Women who are in a high risk programme within the breast screening programme who are diagnosed with breast cancer through the programme will still be invited according to their protocol. It would be their choice not to be invited.	Thank you for this information.
SH	Queen Mary University of London	1	Full	36	1	Risk categories seem suboptimal for assessing appropriate management. An 8% 10 yr risk at age 40y should be considered VERY HIGH and is very uncommon.	Thank you for your comment. However, we disagree. The definitions of 'high risk' including 10-year risk from aged 40 of 8%

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						A 5-8% risk should be considered HIGH RISK and a group where preventive therapy is appropriate to consider. This is 2-3 times the population risk.	have been accepted by the clinical community for a considerable period of time. (These were included in the first FBC guideline (CG14) published in 2004). This would require a major re-classification of risk categories which was not included in the scope of the guideline.
SH	Queen Mary University of London	2	Full	164	6-7	We welcome the support for preventive therapy in the HIGH RISK (5-8% risk in 10 yrs) or VERY HIGH RISK (>8% 10y risk) group, but feel it would be useful to provide examples of which groups of women. For example HIGH RISK includes: Mother or sister with BC before the age of 50. Two first or second degree relatives with BC at any age Atypical Hyperplasia or LCIS Breast Density of >60% These groups were used I the IBIS trial to define women appropriate to have tamoxifen of anastrozole	Thank you for your comment. Risk categories are listed in chapter 2 of the guideline. Thank you for your comment. Examples such as these could be included in the tools for implementation and we will pass your comments to the appropriate team at NICE.
SH	Queen Mary University of London	3	Full	155	40	There is no evidence for the effectiveness of raloxifene in the adjuvant situation	Thank you for pointing out this error in the background text. We have deleted this sentence.
SH	Queen Mary University of London	4	Full	155	41	raloxifene DECREASES the risk of osteoporosis and bone fracture	Thank you for your comment. We have deleted this sentence.
SH	Queen Mary University of London	5	Full	156	11	Update evidence shows raloxifen is LESS effective that tamoxifen (RR=1.24) Vogel et al Cancer Prev Res (Phila). 2010 Jun;3(6):696-706	Thank you for your comment. Vogel 2010 has been added and the evidence statements and tables have been amended accordingly.
SH	Queen Mary University of London	6	Full	156	13	Evidence from MORE/CORE and RUTH on raloxifene not cited (see 'Cuzick et al Lancet. 2003 Jan 25;361(9354):296-300.	Thank you for your comment.This paper did not come up in searches as it predates the current guideline

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							date limits.
SH	Queen Mary University of London	7	Full	158	all	This table is seriously incomplete. 96 month update of IBIS (Cuzick et al J Natl Cancer Inst. 2007 Feb 21;99(4):272-82) and Marsden trial (Powles et al JNCI 2007) missing as well as further data on fractures , cataracts etc from Cuzick et al Lancet 2003. Further update in Lancet due out this month (Cuzick et al)	Thank you for your comment. Cuzick et al 2007 is included in table Poweles et al 2007 was included in the Nelson 2009 systematic review and therefore not appraised separately as it was only relevant to the adverse outcomes part of the question (population was not relevant to the rest of the topic) The Cuzick et al, 2003 paper did not come up in searches, as this predated the current guideline.
SH	Queen Mary University of London	8	Full	159	all	This table is seriously incomplete. See Cuzick et al Lancet 2003 . Jan 25;361(9354):296-300. Further update in Lancet due out this month (Cuzick et al)	Thank you for your comment. This paper did not come up in searches as it predates the current guideline date limits.
SH	Royal College of General Practitioners	1	Full	38	12	I am not aware of the Tools such as family history questionnaires and computer packages exist that can aid accurate collection of family history information and if they are available in primary care.	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	Royal College of General Practitioners	2	Full	51	32	In 2004 NICE guidelines advised Healthcare professionals should respond to women who present with concerns, but should not actively seek to identify women with a family history of breast cancer. This new NICE guidelines suggests a proactive approach is expected from primary care. This will require training and raising awareness in primary care as well as explanation regarding the Manchester scoring system	Thank you for your comment. There have been no change to these recommendation from 2004 and there is no mention of GPs taking up a more proactive approach

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SH	Royal College of General Practitioners	3	Full	53	31	I am not aware of standardised patient information leaflets which also need to be accessible for people with a learning disability or whose first language is not English	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	Royal College of General Practitioners	4	Full	General	General	Are there substantive differences in guidelines between other countries, particularly European countries including Poland? See www.ncbi.nlm.nih.gov/pmc/articles/PMC3186026/	The current draft guidelines now align our position with most European countries where testing thresholds are generally around 10% if they are specified. Testing in Poland is similar to that in the Askenazi Jewish (AJ) population where 3 common mutations are present in the population (0.5% frequency in Poland 2.5% in AJ). As such testing thresholds are much lower in Poland, but this is not for full mutation screening. Testing for AJ mutations in the UK has long had lower thresholds and this has been specified in previous versions of the guideline.
SH	Royal College of Nursing	1	Full	general		The Royal College of Nursing welcomes proposals to update this guideline. It is timely. The document is comprehensive.	Thank you.
SH	Royal College of Nursing	2	Full NICE	140 33	 12	Typographical error - should read 'is **in** line with....'	Thank you for your comment. This amendment has been made.
SH	Royal College of Obstetricians and Gynaecologists	1	Full	87		Section 6.4 – it is disappointing that this section does not mention fertility preservation and the impact that awareness of genetic results may have on this – for example whether to freeze eggs or embryos with or without PGD. This is an important issue for many young women and this is a missed	Thank you for your comment. Whilst we agree this is an important issue, it was not included within the scope of the guideline. Fertility issues often arise in clinical genetic

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						opportunity to mention it.	consultations and genetic counsellors are able to provide advice and information.
SH	Royal College of Obstetricians and Gynaecologists	2	Full	164	6	Final recommendation -stop tamoxifen 3 months before trying to conceive. Nowhere is the increased risk of endometrial polyp formation with tamoxifen discussed and the potential impact of this on future conception. This needs to be made clear if recommendations are that tamoxifen is given to premenopausal women who may wish to conceive in the future with no personal history.	Thank you for your comment. The first recommendation in this section states 'discuss and give written information on the absolute risks and benefits, including side effects of drugs.
SH	Royal College of Obstetricians and Gynaecologists	3	Full	185	1	Should this read Radiotherapy for people	Thank you, we have made this amendment.
SH	Royal College of Obstetricians and Gynaecologists	4	Full NICE	148 1.7.5	Grey Boxed Rec	Increased risk of breast cancer with oral contraceptive use. There are different types of OC of course, some oestrogen containing and others not. Are you able to comment about relative suitabilities (from a cancer perspective)? The long acting reversible contraceptives (LARCs) are increasingly promoted and popular, most containing a progestogen. Is there any advice to be had on the suitability or otherwise of LARCs in this context? Do you wish to refer to the UKME Criteria?	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	Royal College of Obstetricians and Gynaecologists	5	Full NICE	148 1.7.8	Grey Boxed Rec	'..risk reducing oophorectomy..' I presume you mean bilateral salpingo-oophorectomies?	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	Royal College of Obstetricians and Gynaecologists	6	Full NICE	151 1.7.10 et seq	Grey Boxed Rec	HRT prescribing in this group of women is a specialised area and information from trials frequently changes that which is considered appropriate and inappropriate. Given this situation, would you consider making a recommendation that	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to

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						prescribing for these women should be by, or in consultation with a recognised specialist in the menopause (rather than in primary care alone)? I appreciate the two are not necessarily mutually exclusive.	sections that were not updated we are unable to comment.
SH	South East Thames Regional Genetics Service (based at Guy's & St Thomas' NHS Foundation Trust)	1	Full	66	9	This section cites data to suggest that offering BRCA testing to women with triple negative breast cancer under the age of 50 is not cost effective. More recent data (Robertson et al 2012 Br J Cancer) suggests that the probability of such women harbouring a BRCA mutation is >10%. Regardless of cost effectiveness, these data introduce conflict within the guideline, as these women should be offered testing based on likelihood of there being a mutation.	Thank you for your comment. The purpose of the question was not to identify which specific populations should get genetic testing at a 10% threshold, rather it was to determine what carrier probability threshold for genetic testing should be applied. Therefore only evidence comparing different carrier probability thresholds was deemed to be relevant to the clinical evidence review. The Robertson et al paper (2012) was excluded from the clinical evidence review as it did not compare different carrier probability thresholds. This section in the guideline refers to the review of health economic evidence and reports the conclusions of previous studies. The Robertson et al paper (2012) did not report or included a health economic evaluation and was excluded from the economic evidence review for this guideline. The Kwon 2010b study suggested that genetic testing in all women with a personal history of breast cancer under the age of 50 years

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							was not cost effective. However, they suggested that genetic testing in all women with a personal history of breast cancer under the age of 40 years was cost effective. Furthermore, genetic testing was found to be cost effective in both women with triple-negative breast cancer under age 50 and under the age of 40. There is therefore no conflict between Kwon's conclusion with regard to cost-effectiveness of genetic testing in triple negative patients (likely to have carrier risk >10%) aged <50 and the recommendations made by the GDG. The papers identified in the systematic review all had serious limitations, which meant that they were not of high enough quality/relevance to base recommendations on and hence the need for us to do de novo modelling. The de novo modelling conducted has limitations including the pragmatic evaluation of breast cancer as an overall condition, rather than a range of analyses each for a specific breast cancer type. However, where data were available model inputs were selected/derived to represent a

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							range of breast cancer types and hence give a picture of the overall situation for all breast cancers It is the results of this de novo modelling exercise not the data from these previous health economic evaluations which have informed the guidelines. Adjusting the prediction of probability of being a gene carrier for tumour type would make women between 40-50 with triple negative cancer eligible for testing if they also have an affected relative but not without.
SH	South East Thames Regional Genetics Service (based at Guy's & St Thomas' NHS Foundation Trust)	2	Full	91	11-45	This section appears to assume that the current average timeframe of BRCA testing in the UK has been chosen based on evidence benefit. This is not, and has never been the case. BRCA gene testing timeframes have fallen from >12 months to <8 weeks in the last decade. Many laboratories are now capable of producing results within 4 weeks, and times are likely to continue to fall due to technological advances. Although there may be "insufficient evidence to say whether knowledge of mutation status before making decisions about risk-reducing mastectomy influenced outcome", there is also insufficient evidence to say that artificially delaying testing, or referral to genetics services improves outcome. Although testing at the point of diagnosis will not be right for all patients, discussion of the issues with an appropriately qualified clinician should be offered.	Thank you for your comment. The time scale of <4 weeks was chosen to align with the national cancer treatment targets. In women not undergoing neo-adjuvant chemotherapy surgical decisions need to be made within 4 weeks from the point of diagnosis. As such the 4 week interval was an imperative. You have made the comment that the MDT can address these issues quite capably, but it is vital that any such rapid testing is properly assessed before becoming widespread practice.

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						Decisions on breast cancer management are complex and are best made following discussion within the multidisciplinary team. Such teams are well placed to balance surgical, medical, and psychological considerations. Suggesting an arbitrary cut-off of 4 weeks for reporting times is illogical.	
SH	South East Thames Regional Genetics Service (based at Guy's & St Thomas' NHS Foundation Trust)	3	Full NICE	85 28	 1.5.9	These patients are normally managed in secondary care, and are not part of the Nationally agreed service specification for Clinical/Medical Genetics.	Thank you for your comment. We would hope that healthcare professionals in secondary care would advise the unaffected individual to encourage their relative to seek genetic advice.
SH	St George's University of London	1	Full	General		A key problem with the document is the use of the rather nebulous terms "offer" and "consider" which are ambiguous terms and will result in inconsistent interpretation across centres.	Thank you for your comment. 'Offer' is appropriate wording for a recommendation where the GDG is confident that, for the vast majority of people, the recommendation will do more good than harm. 'Consider' is the appropriate wording for a recommendation where the benefit is less certain and where a discussion about risks and benefits is required. Inevitably this may result in inconsistencies of practice that will reflect patient choice. We have added a statement to our methodology section to clarify and define these terms. For further clarification on the use of the terms 'offer' and 'consider' we recommend that you consult the NICE guidance development manual which is available on the NICE website:

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							(http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelinedevelopmentmethods/clinical_guideline_development_methods.jsp). Since all developers of NICE guidance follow this methodology it ensures the use of these terms is consistent across their entire work programme.
SH	St George's University of London	2	Full	General		The pathways proposed focus on unaffected women rather than affected women who are frequently referred from oncology services.	Thank you for your comment. This guideline refers to both unaffected and affected individuals and we hope this is appropriately reflected in the recommendations where we have reviewed the evidence.
SH	St George's University of London	3	Full	116		No surveillance recommendations made for other increased risk syndromes eg Peutz Jeghers, NF, E-cadherin	Thank you for your comment. We have added these groups to the surveillance recommendations. These guidelines refer to the care of people with a family history of breast cancer. There is also no evidence base for screening in these conditions other than based on risk. Risk based screening is already included in this guideline.
SH	St George's University of London	4	Full NICE	42 15	1.1.19	Whilst we agree that risk assessment models can be useful, the advice given in the document does not take into account the fact that these systems are user dependent and rely heavily on the accuracy of the information that is inputted. In addition, these risk assessment models can be complicated to use- we would not recommend their being used in	Thank you for your comment. We did not specifically recommend extending its use in secondary care - we only recommended using these tools where they are currently available. All risk assessment tools are reliant on

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						secondary care.	the user being appropriately trained and the accuracy of the data inputted. We also recommend that if there is a problem with using or interpreting the tools then clinical judgement should be used. We have also made a research recommendation for further development and validation of these models for calculating carrier probability.
SH	St George's University of London	5	Full NICE	85 28	1.5.10 and 1.5.11	Whilst we welcome the introduction of unaffected testing at MS ≥17, we do not agree with the recommendation that it be considered where the unaffected risk is 5-10%. This is because it is not giving clear guidance to centres with the result that there will be inconsistencies across centres. In addition, the burden to our centres of testing these unaffected women will be considerable	Thank you for your comment. The recommendations to consider genetic testing at 5-10% have been removed from the guideline. The GDG agreed that lowering the threshold to 5% would increase the number of patients eligible for genetic testing and potentially overload the existing service. In addition the GDG did not wish to recommend a lower threshold than most other countries worldwide who offer genetic testing.
SH	St George's University of London	6	Full NICE	85 29	1.15.14	We agree that variants of unknown significance should be recorded but we also suggest that a collective database is established where this information can be recorded and shared.	Thank you for your comment. We have amended and expanded this recommendation to include advice on the potential risk and benefits of genetic testing and inform families with no clear genetic diagnosis that they can request review in the specialist genetic clinic at a future date.
SH	St George's University of London	7	Full NICE	91 29	1.5.1	We do not understand why fast track genetic testing should be advised against. There is a very real clinical utility in stratifying management/risk	Thank you for your comment. There is no evidence of any benefit of rapid genetic testing for

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					5	reducing surgical options where a BRCA1/2 mutation is identified prior to surgery.	people newly diagnosed with breast cancer, and therefore a research recommendation was made in order to address this gap. There is no evidence of any benefit of rapid genetic testing for people newly diagnosed with breast cancer, and therefore a research recommendation was made in order to address this gap. Additionally the GDG could not support a recommendation to offer rapid testing on a widespread basis as the systems are not in place to support this. Whilst it was acknowledged that identification of a BRCA1/2 mutation could have significant impact on the choice of primary treatment, a high proportion of triple negative breast cancers now receive neo-adjuvant chemotherapy which allows much more time for test information to be properly assimilated.
SH	St George's University of London	8	Full NICE	116-117 31	 1.6.8	There is no upper age limit for moderate risk breast screening	Thank you for your comment. The GDG have revised the recommendations to clarify the age ranges where surveillance should be available for all the moderate and high risk groups. The GDG have acknowledged in the guideline that there was no evidence specifically relating to surveillance for women aged 70 years and over and could

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							therefore make no specific, evidence- based recommendations. However, the GDG agreed that as these women remained at risk of breast cancer, they should still have access to surveillance. In the absence of any evidence to support enhanced surveillance, the GDG agreed that the best course of action was to recommend that these women should remain in or return to the standard population screening programme.
SH	St George's University of London	9	Full NICE	164 38	1.7.20	Who will take responsibility for prescribing tamoxifen?	Thank you for your comment. This is an issue for implementation and will be highlighted to the Implementation Team at NICE. However the GDG agreed that the oncologist would first prescribe tamoxifen but the GP would take over this responsibility.
SH	St George's University of London	10	Full NICE	164 38	1.7.25	Again "consider" is very unhelpful here and will result in inconsistencies of practice. It would be far more helpful to have more concrete guidance as to ages etc	Thank you for your comment. 'Offer' is appropriate wording for a recommendation where the GDG is confident that, for the vast majority of people, the recommendation will do more good than harm. 'Consider' is the appropriate wording for a recommendation where the benefit is less certain and where a discussion about risks and benefits is required. Inevitably this may result in inconsistencies of

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							practice that will reflect patient choice.
SH	St George's University of London	11	Full NICE	164 38		It is not clear whether tamoxifen should also be offered to BRCA1 carriers?	Thank you for your comment. There was insufficient evidence of a specifically different effect in BRCA gene carriers, so the amended background notes the ER specific risk reduction. Therefore the recommendations have not been amended as the risks should be discussed on an individual basis
SH	St George's University of London	12	Full NICE	55-58 26	Grey Box Rec 1.4.5	Studies have shown that the BRCA1/2 mutation pick up is greater than an threshold value of 10% for TNT <50 rather than 40.	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment. The recommendations that cover this topic state a triple negative breast cancer under the age of 40 years¸ as there is no strong evidence for sporadic TNT at aged 40-49. Please see pages 73-76 of the full guideline.
SH	Surrey, West Sussex and Hampshire Cancer Network	1	Full	91	7	We would welcome wider availability of fast track genetic testing for those individuals where it is apparent at diagnosis that Carrier status would affect decision making (usually surgical).	Thank you for your comment. The guideline makes it clear that genetic testing at any point in time including during the course of primary breast cancer treatment can be offered to people with breast cancer who fulfil the referral criteria. There is no evidence of any

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							benefit of rapid genetic testing for people newly diagnosed with breast cancer, and therefore a research recommendation was made to address this gap.
SH	Surrey, West Sussex and Hampshire Cancer Network	2	Full	158	Table	We are very anxious about the recommendation for Tamoxifen for chemoprevention in moderate risk women before or after the menopause. This table shows that by treating over 10,000 women we prevent 191 breast cancers but cause 124 serious adverse events (endometrial cancer, thromboembolic events, stroke). There is no data on the effect of oestrogen depravation in the premenopausal cohort. More data is required before this recommendation results in Tamoxifen being prescribed to a large population of women who do not have cancer.	Thank you for your comment. The recommendation is not to prescribe tamoxifen routinely but to have a formal discussion of risk and benefits with each individual.
SH	Target Ovarian Cancer	1	Full	general		Target Ovarian Cancer would like to place on record its desire to see a patient centred guide on BRCA related cancers. This is not a patient centred guide but a condition centred guide. Whilst there is value in this update, and we welcome the references to ovarian cancer, it is frustrating that despite the title 'Classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer', the related risks of ovarian cancer, and for that matter prostate cancer, are not even adequately identified, let alone addressed. A person with a BRCA mutation needs to be made aware of the full range of risk they face. As a charity, we come across women, undergoing regular surveillance or preventative surgery who have never been informed about the risk of ovarian cancer. In the instances where they have gone on to develop ovarian cancer, it is a fact that in all	Thank you for your comment. We recognise the issue of ovarian cancer, however the scope of this guideline was restricted to familial breast cancer. The patient pathway will cross refer to the ovarian cancer guideline.

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						likelihood will cost them their lives. Each year approximately 1,000 women will develop ovarian cancer because of an inherited faulty gene. Their chances of survival are much lower, than those diagnosed with breast cancer.	
SH	Target Ovarian Cancer	2	Full	166 9 (KRR)	1	We support this research recommendation	Thank you for your support.
SH	Target Ovarian Cancer	3	Full	22		This algorithm is very unclear, and appears to duplicate information in a number of steps	Thank you. We have simplified the algorithms and removed any duplication. We have presented separate pathways within each algorithm for people with and without a personal history of breast cancer. The algorithm has also been updated to reflect any changes made to the recommendations, and in response to comments received from stakeholders.
SH	Target Ovarian Cancer	4	Full	25		Information about risks of ovarian cancer should be offered on this page, both to those with no personal history of breast cancer, and to those who have, who have strong family histories. Discussion should also take place around potential benefits of prophylactic ovarian surgery in reducing this risk, as well as the risks/benefits of ovarian surgery in relation to contralateral or primary breast cancer.	Thank you for your comment. However, this is not the focus of the guideline. Ovarian surgery, including recommendations on discussing the risks and benefits are covered elsewhere in the guideline.
SH	Target Ovarian Cancer	5	Full	50	3.1	There is no mention here on the provision of information on the risk of developing ovarian cancer, (primary, secondary) ovarian cancer symptoms (primary, secondary), which could be based on www.nice.org.uk/cg122, or the risks/benefits of prophylactic bilateral salpingo oophorectomy in terms of managing ovarian cancer	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.

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						risk (secondary, tertiary)	
SH	Target Ovarian Cancer	6	Full	166	27	The risk of developing ovarian cancer is not quantified. The risks of surgery must be balanced against the future risks of developing breast and/or ovarian cancer.	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	Target Ovarian Cancer	7	Full	169	6	Better wording would be… increased risk of ovarian cancer including fallopian tube and peritoneal cancers	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	Target Ovarian Cancer	8	Full	169	24	Evidence statements do not address the risk reduction in terms of ovarian cancer. This is an important part of the information women should consider.	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	Target Ovarian Cancer	9	Full	180		There is insufficient discussion here of the evidence base about risk, and risk reducing bilateral salpingo oophorectomy, given that the statement Discuss the risks and benefits of risk-reducing bilateral salpingo-oophorectomy with women with a known or suspected to have a *BRCA1*, *BRCA2* or *TP53* mutation. Include in the discussion the positive effects of reducing the risk of breast and ovarian cancer and the negative effects of a surgically induced menopause. **[new 2013]**	Thank you for your comment. We acknowledge that the evidence base was limited and we addressed this in the linking evidence to recommendation section. The GDG agreed it was important, based on their clinical opinion, for women considering risk-reducing surgery to receive information on all the risks and benefits of this surgery, to aid them in making an informed decision.
SH	The British Association of	1	Full	168		We would recommend an addition to this P7 line 15	Thank you for your comment.

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	Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS)			7 (KPI)	15	to include "All reconstructive options both autologous (including free flap reconstruction) and non-autologous reconstructive methods should be offered."	The recommendation states that an individual should have a discussion on their reconstruction options. This discussion would be likely to include your suggestions. We are unable to make amendments to 2004 recommendations when we have not reviewed the evidence.
SH	The British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS)	2	Full	168		Also on P168 we would like there to be an addition to the recommendations. A surgical team with specialist oncoplastic/breast skills in both autologous (including free flap reconstruction) and non-autologous reconstruction should carry out risk reducing surgery and/or reconstruction.	Thank you for your comment. Only the new and updated recommendations in this guideline formed part of the consultation process. As these refer to sections that were not updated we are unable to comment.
SH	The Polyposis registry	1	Full and NICE	General		There is no mention at all of breast screening for Peutz-Jegher's syndrome. This is a dominantly inherited condition due to mutation in the STK11 gene, affecting about 1:200 000. Women with PJS have approximately 50% lifetime risk of breast cancer with median age at diagnosis in 30s. Current European guidelines for management of PJS recommend annual breast screening from age 25-30, including MRI in premenopausal women (Peutz-Jeghers Syndrome: a systematic review and recommendations for management. AD Beggs, AR Latchford, HFA Vasen et al. *Gut* 2010: 59; 975-978). PDF attached. This should be included in the full and NICE guidelines, to ensure that these women have appropriate access to high quality screening.	Thank you for your comment. We have added these groups to the surveillance recommendations. This guideline refers to the care of people with a family history of breast cancer. There is also no evidence base for screening in these conditions other than based on risk. Risk based screening is already included in this guideline.

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SH	The Polyposis registry	2	Full and NICE	General		There is no mention at all of breast screening for Cowden syndrome. This is a very rare dominantly inherited condition due to mutation in the PTEN gene. Women with Cowden syndrome have age adjusted standardised incidence ratio of breast cancer of approximately 25. Current guidelines for management of Cowden syndrome recommend annual breast screening, including MRI in premenopausal women (Lifetime cancer risks in individuals with germline PTEN mutations M Tan, JL Mester, J Ngeow et al. Clin Cancer Res 2012; 18(2): 400-407.). PDF attached. This should be included in the full and NICE guidelines, to ensure that these women have appropriate access to high quality screening.	Thank you for your comment. We have added these groups to the surveillance recommendations. This guideline refers to the care of people with a family history of breast cancer. There is also no evidence base for screening in these conditions other than based on risk. Risk based screening is already included in this guideline.
SH	The Royal College of Radiologists (RCR)	1	Full NICE	42 15	 1.1.19	The RCR notes that the tools to quantify the risk and the definitions of at risk patients are made clearer in this guideline. However, we suggest a web-link to access BOADICEA or Manchester score could have been helpful.	Thank you for your comment. We have included hyper linked web addresses.
SH	The Royal College of Radiologists (RCR)	2	Full NICE	85 28	 1.5.10	For those with no personal history of breast cancer, the BRCA1 and 2 carrier probability figures are clear and they are particularly helpful for those whose relative is unavailable for testing. However the RCR suggests it may not always be easy to estimate accurately the risk figure of that relative and the guidelines could have elaborated on that.	Thank you for your comment. Testing is offered in specialist genetics clinics where familiarity with estimating probability should be part of the expert knowledge base. This is also covered under chapter 2.
SH	The Royal College of Radiologists (RCR)	3	Full NICE	91 29	 1.5.15 – 1.5.17	The RCR notes that the timings and circumstances around the genetic testing appear appropriate and practical.	Thank you.
SH	The Royal College of	4	Full	116-		We welcome the clarification on the role of	Thank you for your comment. We

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	Radiologists (RCR)		NICE	117 30	1.6.2	Ultrasound in screening but suggest that claustrophobia could have been addressed more fully. While the RCR agrees that the proportion of patients requiring screening MRI is small - and those who are claustrophobic is even smaller – we felt it would have been helpful to mention such situations.	agree there may be other situations in addition to claustrophobia which we have used as an example. The issue of when MRI is not suitable was not included in this question however we have included claustrophobia as a recognised concern.
SH	The Royal College of Radiologists (RCR)	5	Full NICE	116-117 31	1.6.9	The RCR notes that the new additions for 2013 on surveillance appear appropriate but we feel they would increase the workload of already overstretched MRI services in most hospitals. Also we feel that an annual MRI for all women aged 30-49 years, including those who haven't had mutation testing, may be a bit extreme.	Thank you for your comment. This recommendation remains unchanged from the 2006 guideline, and there was no new evidence to support a change. This category was included because of a suggestion that women should be encouraged to undertake genetic testing in order to qualify for MRI surveillance. The number of women in this category will be very small.
	The Royal College of Radiologists (RCR)	6	Full NICE	116-117 & 137 33/34	All 1.6 16 – 1.6.19	Support - including psychological, education and continuous proper communication - is a welcome addition.	Thank you.
	The Royal College of Radiologists (RCR)	7	Full NICE	116-117 & 137 35	1.6 21 – 1.6.23	Stress on the quality and standards of surveillance are an important point.	Thank you, we agree.
	The Royal College of	8	Full	116-		The RCR questions why the guideline suggests not	Thank you for your comment. We

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	Radiologists (RCR)		NICE	117 & 137 35	1.6 25	offering surveillance after bilateral mastectomies.	feel that having risk reducing surgery means you are no longer in the risk category for screening.
	The Royal College of Radiologists (RCR)	9	Full NICE	164 38	1.7.20	The RCR feels that the guidance about chemoprevention may be both controversial and challenging. We understand that the evidence is divided, even though the practice is long established in North America. We would question the position for patients with a history of thromboembolic disease or uterine cancer.	Thank you for your comments. We believe the recommendations address these concerns.
	The Royal College of Radiologists (RCR)	10	Full NICE	175 42	1.7.52	We suggest that the use of HRT after bilateral salpingo-oophorectomy in high risk patients with no history of breast cancer should be clearer and should only apply to those patients who have already had bilateral mastectomies.	Thank you for your comment. This would exclude a proportion of women that may be entitled to HRT and there is no evidence to suggest that HRT increases the risk of breast cancer in women under 50 who have had their ovaries removed. See Pg 175 Line 28-29
	The Royal College of Radiologists (RCR)	11	Full NICE	187 44	1.7.64	The RCR feels that management of TP53 mutation positive patients diagnosed with breast cancer is well covered.	Thank you for your comment.
	The Royal College of Radiologists (RCR)	12	Full	116		A mortality benefit from family history screening is assumed even though there is little or no evidence for this. Given the lack of a size outcome relationship in basal cancers this is of particular concern when screening BRCA 1 carriers. This is in direct contrast to the proven mortality benefit in BRCA 1 carriers of prophylactic mastectomy (the benefits of which seems rather underplayed in this document). Investigating the mortality benefit of screening does not even figure in the areas recommended for further research. Assuming mortality benefits from	Thank you for your comment. Research in this area would also be impractical. Any study undertaken would have to be a randomised controlled trial and recruitment would be extremely difficult. In order to get meaningful data you would need a very high number of participants in the trial and at least 30 years of follow up.

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						extrapolating from prognostic indicators is a dangerous business and should not be taken as proof of benefit due to the influence of lead time bias. The recommendation for annual mammography for moderate risk women to age 70 is not evidence based. The decision to screen should be taken on risk grounds, the frequency should be based on the lead time achieved. The lead time of screening women over 50 is 3-5 years and there is no evidence that this is reduced in moderate risk women. The appropriate interval is therefore 2 yearly (or maybe 18 monthly to fit in with NHSBSP 3 yearly screening). More frequent screening is associated with a large rise in false positive outcomes.	Thank you for your comment. The GDG have revised the recommendations to clarify the age ranges where surveillance should be available for all the moderate and high risk groups. The GDG have acknowledged in the guideline that there was no evidence specifically relating to surveillance for women aged 70 years and over and could therefore make no specific, evidence-based recommendations. However, the GDG agreed that as these women remained at risk of breast cancer, they should still have access to surveillance. In the absence of any evidence to support enhanced surveillance, the GDG agreed that the best course of action was to recommend that these women should remain in or return to the standard population screening programme.
SH	The Society and College of Radiographers	1	Full	116		The consultation is well thought out but the practicalities of the increased level of imaging surveillance will put a strain on many breast imaging units. - Annual MRI on high risk patients will be difficult to accommodate - Mammographic surveillance is increased to annual from 40 years upwards. We currently discharge to NHSBSP at 50. The guidance does not make it clear where this surveillance will	Thank you for your comments. The recommendations for surveillance remain mostly unchanged from the 2004 and 2006 guidelines. This is an implementation issue and will be highlighted to the Implementation Team at NICE

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						take place, in secondary care or the local screening service. Not all screening / symptomatic units are within one hospital or even Trust. - Referral to genetics, already takes many weeks for results due to demand on the service. - The guidance suggests surveillance by ultrasound if MRI not possible, this can be falsely reassuring.	We hope that clearer guidance will make this service quicker and more efficient. Thank you, we agree, and have now addressed this within the LETR paragraph.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	1	Full	General		Overall these draft guidelines are inconsistently written, the language does not flow well. The document does not appear to have been proofread for inconsistencies prior to submission for the consultation process.	Thank you for your comments. Developing this guideline has presented the GDG and NCC-C with a variety of challenges. What we were asked to do was update the existing familial breast cancer guideline (CG14/14) and to incorporate a new set of recommendations on the management of people with a personal history of breast. However the GDG were not permitted to change any of the recommendations from topics in CG14/41 that were not updated. These topics were clearly presented and explained in the guideline scope. As a result there are places in the guideline that are different in style and presentation compared to the updated and new sections. We have attempted to provide sufficient information in Chapter 2

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							to enable the reader to understand and interpret the more specific recommendations later in the document. The presentation and order of each chapter is consistent, however the depth and content does vary as we were not able to significantly alter sections we were not updating. Nevertheless the GDG has attempted to improve the structure and flow of the guideline and has tried to ensure the language, terminology and style are consistent throughout.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	2	Full	General		Through out the document there does not seem to be any consistency in the use for the terms "mutation", "faulty gene" and "variant"	We have tried to be consistent throughout the guideline when using the terms, and we have reviewed the guideline to ensure this is the case.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	3	Full	1	1	We suggest the title could be amended to: Familial breast cancer: Assessment and management of individuals with or at risk of breast cancer due to a family history.	Thank you for your comment. We are unable to amend the title. This guideline is an update of an existing guideline (CG14/41) that now incorporates a new short guideline and the title and remit was given to NICE by the Department of Health.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	4	Full	22	4	These algorithms (page 22-25) contain a number of inconsistencies and need to be re-written to provide clearer guidance.	Thank you. We have simplified the algorithms and removed any duplication. We have presented separate pathways within each algorithm for people with and without a personal history of breast cancer. The algorithm has

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							also been updated to reflect any changes made to the recommendations, and in response to comments received from stakeholders.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	5	Full	22		The first line of this algorithm which refers to a patient presenting to the GP with breast symptoms should be removed. Most patients to whom these guidelines apply will be presenting to primary care because of concerns due to their family history. The management of breast symptoms should be covered by different guidelines.	Thank you for your comment. We agree and have simplified this statement to read 'A person presents to their GP with concerns regarding their family history'.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	6	Full	23	2	It would seem logical for it to be easier for a person who has actually had breast cancer to meet the criteria for referral to tertiary services than for referral of a person who does not have a personal history of breast cancer.	To avoid any confusion we have simplified the algorithms and removed any duplication. We have presented separate pathways within each algorithm for people with and without a personal history of breast cancer. The algorithm has also been updated to reflect any changes made to the recommendations, and in response to comments received from stakeholders.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	7	Full	25	1	The recommendations for the extent of family history needed to be taken by primary, secondary and tertiary care is inconsistent.	Thank you for your comment. We believe these are consistent with the care settings in terms of the extent of the recommendations.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	8	Full	25	1	In other sections of the guidance the recommendation is for genetic testing to be offered to those with a mutation carrier probability of 5% or over but the recommendation in the box entitled "Breast cancer risk assessment" suggests referral for genetic counselling and genetic testing if the mutation carrier probability is greater than 10%.	The recommendations to consider genetic testing at 5-10% have been removed from the guideline. The GDG agreed that lowering the threshold to 5% would increase the number of patients eligible for genetic testing and potentially

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						This is inconsistent with bullet point 3 in the box below that says genetic testing should be offered to those with a carrier probability of 5-10%. The final bullet point in that box suggests offering genetic testing to an individual with a carrier probability of 2.5%.	overload the existing service. In addition the GDG did not wish to recommend a lower threshold than most other countries worldwide who offer genetic testing. We have checked the original algorithm and could not find reference to a carrier probability of 2.5%.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	9	Full	25	1	The Manchester scores used throughout this algorithm are inconsistent.	We have removed reference to the Manchester Score from the guideline as it is one of several methods of providing an estimate of probability of finding a mutation, and therefore no does warrant being given special attention.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	10	Full	25	1	The box in the right-hand column which asks whether a genetic test has been requested within 4 weeks of diagnosis seems misplaced and contradicts the bullet points in the box below it.	Thank you for your comment. We agree and have simplified the algorithm to ensure all boxes are now appropriately connected, including genetic testing.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	11	Full	25	1	The boxes to the left of the algorithm regarding chemoprevention and HRT use appear to be floating. It is not clear where these recommendations fit in the pathway.	Thank you for your comment. We agree and have simplified the algorithm to ensure all boxes are now appropriately connected, including chemoprevention and HRT. The algorithm has also been updated to reflect any changes made to the recommendations, and in response to comments received from stakeholders.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service	12	Full	25	1	Regarding chemoprevention, the last bullet point should also include a recommendation to stop tamoxifen prior to surgical procedures.	Thank you for your comment. The recommendations do include stopping tamoxifen six weeks prior to surgery. See page 184 of the

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	dept.)						full guideline. We have also simplified this algorithm and a cross reference to the chemoprevention recommendations has now been included.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	13	Full	85	10	We feel that these recommendations are written in a confusing manner and therefore do not provide guidance which can be easily understood by the reader.	Thank you for your comment. We have amended these recommendations and included appropriate sub-headings for simplicity.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	14	Full	85	10	It is not clear for whom the recommendations for testing have been provided. They are not necessarily useful to tertiary care services and are not relevant to primary care.	Thank you for your comment. These recommendations are relevant across all NHS care settings however they are intended to be used in the specialist genetic clinics (tertiary care) (see also the algorithm on page 50).
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	15	Full	85	10	The type of family history acceptable for testing seems very broad. Almost any extent of family history seems acceptable. The first two groups for whom recommendations have been given appear to be very similar.	Thank you for your comment. We have amended these recommendations based on feedback from stakeholders and have included appropriate sub-headings for simplicity. The recommendations to consider genetic testing at 5-10% have been removed from the guideline. The GDG agreed that lowering the threshold to 5% would increase the number of patients eligible for genetic testing and potentially overload the existing service. In addition the GDG did not wish to recommend a lower threshold than

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							most other countries worldwide who offer genetic testing.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	16	Full	85	10	Bullet point 2 suggests offering testing to a relative who has not been referred to tertiary care.	Thank you for your comment. The recommendations to consider genetic testing at 5-10% have been removed from the guideline. The GDG agreed that lowering the threshold to 5% would increase the number of patients eligible for genetic testing and potentially overload the existing service. In addition the GDG did not wish to recommend a lower threshold than most other countries worldwide who offer genetic testing.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	17	Full	85	10	We feel it is very important that these recommendations state clearly that the most informative strategy is for genetic testing to be undertaken in an individual who has had cancer, rather than in an unaffected relative.	Thank you for your comment. This issue has been covered in the background of section 6.1 in the full guideline (page 88).
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	18	Full	85	10	The use of Manchester score equivalents does not appear to be consistent between different parts of the recommendations. No obvious 5-10% equivalent is provided by the Manchester score.	We have removed reference to the Manchester Score from the guideline as it is one of several methods of providing an estimate of probability of finding a mutation, and therefore no does warrant being given special attention. The model was based on a percentage threshold which we have retained for consistency.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	19	Full	85	10	If genetic testing is to be provided by tertiary care services to individuals with a carrier probablility as low as 5% (a carrier probablility which is just over the probability of detecting a mutation by chance) this will provide a significantly increased workload pressure on tertiary services, this does not appear	The recommendations to consider genetic testing at 5-10% have been removed from the guideline. The GDG agreed that lowering the threshold to 5% would increase the number of patients eligible for

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						to have been addressed.	genetic testing and potentially overload the existing service. In addition the GDG did not wish to recommend a lower threshold than most other countries worldwide who offer genetic testing.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	20	Full	87	18	This first paragraph is not necessary as the subsequent text gives the context for rapid genetic testing.	Thank you for your comment. We disagree – this paragraph sets out the objectives for this topic.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	21	Full	91	7	These are reasonable, clear and succint recommendations. We agree with these recommendations.	Thank you.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	22	Full	118	3	Table 7.5 We felt overall this table was a helpful and clear format for presenting the recommendations regarding surveillance.	Thank you, we agree.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	23	Full	118	3	Based on previous data, the appropriateness of mammography in TP53 mutation carriers after the age of 50 years is not clear.	Thank you for your comment. We agree and have amended these recommendations to say 'do not offer mammographic surveillance to women of any age with a known TP53 mutation'.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	24	Full	118	3	The recommendations for Group1 – those at moderate risk (who are by far the largest group for whom this table is relevant) is vague regarding recommendations in those aged over 50 years. The guidance for Groups 2-5 is much clearer and better defined. The guidance for those over 50 years at Moderate risk, in its current form is not defined enough and could lead to inequitable access to surveillance for patients in different geographical	Thank you for your comment. 'Offer' is appropriate wording for a recommendation where the GDG is confident that, for the vast majority of people, the recommendation will do more good than harm. 'Consider' is the appropriate wording for a recommendation where the benefit

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						areas. The guidance needs to be clearer to avoid this.	is less certain and where a discussion about risks and benefits is required. Inevitably this may result in inconsistencies of practice that will reflect patient choice.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	25	Full	164	3	The recommendations for the use of tamoxifen and raloxifene in chemoprevention will have an economic impact not only in terms of the cost of the drugs but the greater impact will be due to the need to educate healthcare professionals and patients regarding the potential risks and benefits of the use of these drugs for this purpose. In this economic climate the lack of some estimation of the cost of this intervention seems to be a major omission.	Thank you for your comment. We agree. The GDG decided to carry out a cost-consequence analysis to estimate the incremental costs and outcomes associated with offering chemoprevention compared to current practice. The results of this analysis can be found in the full health economic evidence review. Based on these data the GDG concluded that the costs of preventing a case of breast cancer are likely to be considered acceptable from an NHS perspective.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	26	Full	164	6	Regarding bullet point 1, who would be expected to produce the written inforamtion? Would each centre be expected to do this individually? Which healthcare professionals should be providing this information – this needs to be made clearer.	Thank you for your comment. Each centre would be expected to develop their own information unless there is already nationally developed written information advice. The Guideline Group did not consider the question of which healthcare professionals should be providing the information. This will be an issue that each centre will need to address itself.
SH	University Hospitals Southampton NHS	27	Full	164	6	Regarding chemoprevention in general, who would be expected to prescribe these drugs? Would it be	Thank you for your comment. The GDG agreed that the

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
	Foundation Trust (Wessex Clinical Genetics Service dept.)					healthcare professionals from primary, secondary, or tertiary care? If the information giving and prescribing for high-risk women alone, is expected to be performed by Clinical Genetics services this would create a significant increase in workload for these services. If women at moderate risk are also to be offered chemoprevention, tertiary services may not be able to meet the increased demand.	oncologist would first prescribe tamoxifen but the GP would take over this responsibility. Many of the staff in secondary care services would be familiar with tamoxifen compared to those in tertiary genetic services due to its use in treating breast cancer patients, so either could provide it. Knowledge about the use of tamoxifen or raloxifene as a chemopreventative agent would be required at all levels of care.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	28	Full	164	6	The recommendation does not state the age from which chemoprevention should be considered/prescribed. This is an important omission.	Thank you for your comment. The GDG agreed not to set a minimum age limit for accessing tamoxifen or raloxifene, as they did not want to prevent young women from having access to preventative treatment as there may be some who wish to discuss options other than risk reducing surgery.
SH	University Hospitals Southampton NHS Foundation Trust (Wessex Clinical Genetics Service dept.)	29	Full	164	6	Before the recommendation for prescribing tamoxifen/raloxifene in moderate risk women is made it would be useful for more research to be performed looking at the reduction in breast cancer risk in this cohort specifically, particularly regarding the extent of cancer risk reduction in relation to the risk of significant side effects.	Thank you for your comment. The evidence from the chemoprevention trials is mostly based on moderate risk women not on high risk gene carriers.

These organisations were approached but did not respond:

AbbVie
Action Cancer
African Health Policy Network
Allocate Software PLC
Amgen UK
Association for Family Therapy and Systemic Practice in the UK
Association of Anaesthetists of Great Britain and Ireland
Association of British Insurers
Association of Clinical Pathologists
Astrazeneca UK Ltd
Ataxia Telangiectasia Society
BME cancer.communities
Boehringer Ingelheim
Boots
Bradford District Care Trust
Breast Cancer UK
Breast Screening QA Reference Centre
Breast Test Wales
Bristol and Avon Chinese Women's Group
British Dietetic Association
British Medical Association
British Medical Journal
British National Formulary
British Nuclear Cardiology Society
British Psychological Society
BUPA Foundation
C. R. Bard, Inc.
Cambridge University Hospitals NHS Foundation Trust
Camden Link
Cancer Network User Partnership
Cancer Research UK
Cancer Services Co ordinating Group
Cancer Voices
Capsulation PPS
Capsulation PPS
Care Quality Commission (CQC)
Central South Coast Cancer Network
Cepheid Uk Ltd
Clarity Informatics Ltd
CLIC Sargent
Community District Nurses Association
Covidien Ltd.

Croydon Health Services NHS Trust
Daiichi Sankyo UK
Department for Communities and Local Government
Department of Health, Social Services and Public Safety Northern Ireland
Dorset Primary Care Trust
Dudley Group Of Hospitals NHS Foundation Trust
East and North Hertfordshire NHS Trust
East Midlands Cancer Network
Economic and Social Research Council
Energy Therapy World Wide Net
FaHRAS Ltd
FBA and Brook
Five Boroughs Partnership NHS Trust
George Eliot Hospital NHS Trust
Gloucestershire Hospitals NHS Foundation Trust
Gloucestershire LINk
Great Western Hospitals NHS Foundation Trust
Greater Midlands Cancer Network
Hammersmith and Fulham Primary Care Trust
Health Protection Agency
Health Quality Improvement Partnership
Healthcare Improvement Scotland
Hindu Council UK
Hockley Medical Practice
Hull and East Yorkshire Hospitals NHS Trust
Institute of Biomedical Science
Integrity Care Services Ltd.
International Early Pregnancy Research Group
Johnson & Johnson Medical Ltd
KCARE
Kent & Medway Cancer Network
Lancashire Care NHS Foundation Trust
Lancashire Teaching Hospitals NHS Trust
Liverpool Primary Care Trust
Luton and Dunstable Hospital NHS Trust
Macmillan Cancer Support
Medicines and Healthcare products Regulatory Agency
Ministry of Defence
National Cancer Action Team
National Cancer Intelligence Network
National Clinical Guideline Centre
National Collaborating Centre for Cancer
National Collaborating Centre for Mental Health
National Collaborating Centre for Women's and Children's Health

National Council for Palliative Care
National Hereditary Breast Cancer Helpline
National Institute for Health Research Health Technology Assessment Programme
National Patient Safety Agency
National Public Health Service for Wales
National Radiotherapy Implementation Group
National Treatment Agency for Substance Misuse
NHS Clinical Knowledge Summaries
NHS Connecting for Health
NHS County Durham and Darlington
NHS Direct
NHS England
NHS Hertfordshire
NHS Plus
NHS Sheffield
NHS Sussex
NHS Warwickshire Primary Care Trust
NICE technical lead
North and East London Commissioning Support Unit
North of England Cancer Network
North Trent Cancer Network
Northern Ireland Cancer Network
Northern Ireland Regional Genetics Service
Nottingham City Council
Nottingham City Hospital
Nova Healthcare
Oxford Health NHS Foundation Trust
Oxfordshire Primary Care Trust
Peninsula Cancer Network
Peninsula Clinical Genetics Service
Pfizer
Primary Care Pharmacists Association
Public Health Agency
Public Health Wales NHS Trust
QResearch
Rarer Cancers Foundation
Roche Diagnostics
Roche Products
Royal Berkshire NHS Foundation Trust
Royal College of Anaesthetists
Royal College of General Practitioners in Wales
Royal College of Midwives
Royal College of Paediatrics and Child Health
Royal College of Paediatrics and Child Health , Gastroenetrology, Hepatology and Nutrition

Royal College of Pathologists
Royal College of Physicians and Surgeons of Glasgow
Royal College of Psychiatrists
Royal College of Surgeons of England
Royal Free Hospital NHS Foundation Trust
Royal Marsden NHS Foundation Trust
Royal Pharmaceutical Society
Royal Society of Medicine
Royal Surrey County Hospital NHS Trust
Sandoz Ltd
Sanofi
Scottish Intercollegiate Guidelines Network
Sheffield Teaching Hospitals NHS Foundation Trust
Shropshire & Mid Wales Cancer Forum
Social Care Institute for Excellence
Society for the Protection of Unborn Children
Solent NHS Trust
South Asian Health Foundation
South London & Maudsley NHS Trust
South Staffordshire Primary Care Trust
South Wales Cancer Network
South West Thames Regional Genetics Service
South West Yorkshire Partnership NHS Foundation Trust
Southport and Ormskirk Hospital NHS Trust
St Mary's Hospital
Step4Ward Adult Mental Health
Sussex Cancer Network
Teva UK
The Association for Cancer Surgery
The Association for Clinical Biochemistry & Laboratory Medicine
The British In Vitro Diagnostics Association
The Hindu Forum of Britain
The National LGB&T Partnership
The Rotherham NHS Foundation Trust
The University of Glamorgan
UCL Partners
UCL/UCLH Institute for Women's Health
UK Cancer Genetics
UK Clinical Pharmacy Association
University Hospitals Birmingham
University Hospitals Coventry and Warwickshire NHS Trust
University of Nottingham
Walsall Local Involvement Network
Welsh Government

West Midlands Ambulance Service NHS Trust
Western Cheshire Primary Care Trust
Western Sussex Hospitals NHS Trust
Westminster Local Involvement Network
Wirral University Teaching Hospital NHS Foundation Trust
York Hospitals NHS Foundation Trust
Yorkshire Ambulance Service NHS Trust
Yorkshire Cancer Network