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Microtest Diagnostics	1	23	2.2.2	The Microtest description contains incorrect information and follows a different content template than the ISAC descriptions which makes it difficult to understand the similarities and differences of the two microarrays. We suggest to add a first section that describes microarray technologies in general (2.2), followed by one section that describes the ISAC system (2.2.2) and one for Microtest (2.2.3). See Appendix 1 for a draft updated version.	Appendix 1 contains a complete re-write of section 2.2. of the background section of the report. We do not consider that it would be appropriate to replace sections of our report with sections written by Microtest diagnostics. It is not clear exactly which information the Microtest believe to be incorrect. The format and layout of the introduction is an issue of style preference, but we will endeavour to correct any factual errors ahead of publication if full details are provided.
	2		References	Updated/new Microtest references [155,210], see Appendix 2 in attached document. Both studies include “patients with difficult to manage allergies” tested with 4 allergy methods (SPT, ImmunoCAP, ISAC and Microtest). [210] is accepted for publication, ePub ahead of print. This reference includes both microarrays’ agreement with SPT. The sensitivity/specificity against SPT can be calculated if needed, however, we do not believe any journal reviewers would accept a publication where the sensitivity and specificity measures are based on true status defined by SPT. Therefore the outcome measure “positive/negative concordance with	The information supplied in appendix 2 is not sufficient to determine whether reference [155] would have met the inclusion criteria of our systematic review. As a minimum, a more detailed definition of how ‘Dr’s diagnosis’ was reached would be needed. Additional data supplied at this late time point cannot be included in the main report. However, if a copy of the manuscript is provided to NICE, we would be happy to look at this ahead of the DAC.

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				SPT" was used instead. [155] Abstract published in Allergy, Sept 2015. Article manuscript to be submitted in Dec. Results and methods sections are finalized. Data on sensitivity/specific as defined by physician's diagnosis, as well as the added value of microarray testing are included. The manuscript may be shared with NICE confidentially upon request.	It is for the committee to decide if and how this material should be considered.
	3	24	Table 1	Information regarding a method's ability to measure IgE abs to allergen components and/or whole allergen extracts is lacking. This is a uniqueness and an added value of microarray testing compared to skin prick testing.	Opinion only – no response required.
	4	39	Study design	General question/comment: How is the diagnostic performance/accuracy of a microarray test (sensitivity and specificity) best estimated? The best case scenario would be to compared the result with challenge data. However, challenge data to a broad panel of food allergens is difficult and costly. Challenge test to inhalant allergens is difficult/unusual. On p.39 it is stated that the accuracy of clinical reactivity should be calculated as true status defined by SPT, allergen challenge or response to immunotherapy. We believe Drs diagnosis should also be listed as an accepted substitute maker for the true status.	As noted in section 2.6 of the protocol for this assessment, we do not believe that diagnostic performance/accuracy data alone can provide sufficient evidence to support the clinical utility of multiplex allergen testing. Where accuracy data are reported, we do not believe that 'Dr's diagnosis' alone constitutes an adequate definition of the reference standard; some objective measure such as response to challenge testing or clinical follow-up would be required.

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	5	93	Flowcharts	General question/comment: We believe there is no data in the literature supporting material clinical difference in diagnostic effectiveness between SPT and sIgE titre measurement. Does NICE/International guidelines support the flowchart on page 93 that indicates that sIgE tests can not be used to confirm allergy while SPT can?	Opinion only – no response required The presence of antibodies in plasma does not necessarily mean there is a corresponding allergy only that a patient is sensitised. Please note that the flowcharts are purely theoretical and as stated in the report (just above the flowchart) *"it is unclear whether this theoretical diagnostic pathway (based on clinical expertise and literature) is representative of current UK clinical practice in all secondary or tertiary care settings."* The reason sIgE was assumed to rule out allergies (and not to confirm allergies) is because a positive diagnosis, based on IgE (single or multiplex testing) is always confirmed by a clinical response test (SPT or challenge testing); IgE positive shows the presence of an antibody, which is not the same as the presence of an allergic response.
	6		Objective 4	We believe recombinant allergen components are usually more expensive than traditional allergen	It is not completely which costs the respondent is referring to, as no cost of £13

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				extract-based tests. Is this correct? If yes, is the cost of £13 valid in the cost simulation model? **The simulation results indicate that Microarray testing** will be an efficient test alternative when > 10 (or 13) allergens INCLUDING recombinant allergen components are requested. It will be an efficient test alternative from a cost, sample volume and information point of view (SPT can not provide the information gained by allergen component testing). (Remark: Traditional allergy testing using whole allergen extracts provide non-detailed information (compare with traditional, low-resolution X-ray images), while microarray results including allergen components increase the resolution and provide more detailed information (compare with modern high-resolution PET scans). Both are valuable tools in the diagnostic process, however, high-resolution tools like PET-scans and microarray tests allows for better-informed decisions.	has been used. The cost of £12 per allergy for sIgE, used in the cost simulation model, was taken from NICE CG116 (2011).
	7			General comment: Studies on “patients with difficult to manage allergic dicease” The definition of the patient category is unclear or	The population with difficult to manage allergic disease was defined as people who are allergic to two or more allergens and/or have allergies to unknown sources.

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				does not match the way patient cohorts have been described in the literature. We believe some/many of the referenced studies do include poly-sensitized patients with difficult to diagnose/manage allergies although it may not be stated clearly in the manuscript since this terminology is not commonly used. Eg the studies by Heaps (idiopathic analphylaxis), Luengo (severly multi-sensitized food and inhalation allergies), Konradsen (children with problematic asthma and poly-sensitization including both food and inhalation allergens), Hong (patients with anaphylactic reactions to peanut) all include patients with difficult to diagnose and manage allergies. See Appendix 3 for more studies.	However, it should be noted that studies that did not specify a population with difficult to manage allergic disease or polysensitisation were not excluded (see section 3.2.1 Inclusion and exclusion criteria). Our searches identified both of the articles cited in appendix 3 and neither article met the inclusion criteria for our systematic review, as specified in the assessment protocol.
	8	14	Objective 1 and 2	Are there published studies on SPT or ImmunoCAP demonstrating the effect of testing on the clinical outcome or treatment effect?	An assessment of the clinical effectiveness of SPT or single IgE testing was outside the scope of this project. The limited available data on the clinical effects of ImmunoCAP ISAC testing are summarised in section 3.2.4
	9	117	6. Conclusion	If no recommendations for service provision can be made at this stage it would be of value if the report specifies the major concerns and what additional information is required for a future recommendation of	The report currently contains outline research recommendations. Further details are for discussion by the committee.

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				the service. For example, 1) Is the accuracy of ISAC/Microtest a major concern? What data would be needed to overcome this issue? Should sensitivitity and specificity data be based on physician's diagnosis, challenge data, ImmunoCAP and/or SPT? Do all allergen sources on the chip need to be covered for ISAC/Microtest? 2) Is the clinical value of ISAC/Microtest a major concern for a recommendation? What type of additional data is required to overcome this issue? 3) Is the cost-effectiveness of ISAC/Microtest a major concern if the test is reimbursed for patients where >X (X can for example be 10) allergens needs to be tested?	
	10	59		Last sentence: "However, it should be noted that the addition of ImmunoCAP® ISAC also resulted in the identification of large numbers of sensitisations that were not considered to be associated with the anaphylaxis, i.e. **large numbers of clinically false positive test results**." Is the bold text a correct interpretation of the study results? These positive results did not explain the anaphylactic reaction, but they may be related to other	We agree with the consultee's point; the results are correctly described as clinically false positive with respect to anaphylaxis, however, it is also correct to say that positive results may have been associated with other allergic symptoms. We will amend the text ahead of publication to reflect this point.

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				allergic symptoms of the patients e.g. rhinitis, and may therefore not be false positive results.	
Thermo Fisher Scientific	11	4	Abstract	*Text in DAR* Objectives To evaluate multiplex allergen testing (devices which can measure the presence of multiple IgE antibodies in a patient's blood at the same time), by assessing: 1) clinical effectiveness (allergy symptoms, incidence of acute exacerbations, mortality, adverse events of testing and treatment, healthcare presentations or admissions, health-related quality of life) 2) effects on treatment (diet, immunotherapy medications, other potential testing) 3) any additional diagnostic information provided by multiplex allergen testing 4) cost-effectiveness (cost of different assessment strategies). *Thermo Fisher Scientific response* Thermo Fisher Scientific acknowledges the thorough, systematic literature search and analysis performed in	The publications cited are not primary studies and do not provide additional data. Neither publication meets the criteria for inclusion in the systematic review. The specific position points noted by Thermo Fisher would be covered by the scope of the review, had any data been available.

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				accordance with the NICE scoping document for this appraisal. The conclusions made follow logically from the data evaluated. Based on a review and consideration of the report from the evidence review group, and the recent availability of peer-reviewed data that were not accessible to the group at the time of their searches, we ask NICE to consider this information in addition to that contained in the report, and to consider a re-evaluation of the conclusions (see next paragraph). We also ask NICE and the evidence review group to take into account our comments on some of the descriptions and context for diagnostic tests as described elsewhere in this document. We ask NICE to consider the World Allergy Organization (WAO) consensus positioning from 2013 (Canonica et al. World Allergy Organization Journal 2013;6:17) and assess the value of this emerging technology in the three areas highlighted in the consensus paper: • aiding the diagnostic process in cases of complex sensitisation (to 2 or more allergens, to differentiate genuine from cross sensitisation);	

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				• to estimate the level of severity to potentially avoid challenge testing; • to improve the identification of patients who might require specific immunotherapy (SIT) Specifically, our overall position for the Immuno Solid-phase Allergy Chip (ISAC) is as follows: • ISAC, when used in addition to skin prick test (SPT) and IgE testing, can provide additional diagnostic insight in line with WAO expert opinion and consensus. • Thermo Fisher Scientific does not consider ISAC as an alternative to either of the current gold standard allergen sensitisation tests (SPT and IgE detection). We also draw your attention to a recent review of molecular allergy diagnostics by Hamilton and Kleine-Tebbe (Curr Allergy Asthma Rep 2015; e-pub ahead of print), who describe how allergen components/extracts can help achieve diagnostic clarity by selectively detecting low abundance allergens in addition to the areas highlighted by WAO. Additionally, this approach is in line with NICE guidance on the appraisal of diagnostics	

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				(https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-diagnostics-guidance/Diagnostics-assessment-programme-manual.pdf), which states that the "principal output from diagnostic tests is usually information." Information is the third of the stated objectives in the report. We ask that NICE and the evidence review group consider our request in light of the additional information provided here and throughout this response document (see responses to comments 2 and 33 for further information).	
	12	4-5	Abstract	*Text in DAR* The very limited available data indicated that the addition of multiplex allergen testing (ImmunoCAP® ISAC) to standard diagnostic work-up can change the clinicians' views on the diagnosis, management and treatment of patients. There was some indication that the use of ImmunoCAP® ISAC testing may be useful to guide decisions on the discontinuation of restrictive diets, the content of allergen specific immunotherapy (SIT) prescriptions, and whether or not patients should receive SIT.	We have obtained copies of all three of the 2015 publications cited. None of these articles meet the inclusion criteria for our systematic review, as specified in the approved protocol, for this assessment (see section 3.1.2 of the report). Simpson et al. 2015 and Custovic et al. 2015 are similar studies by the same group. Both are population studies mapping longitudinal patterns of IgE response, as measured using ImmunoCAP ISAC 112. They do not provide any measure of the effects of using

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				Thermo Fisher Scientific response: Based on our response to comment 1 above, we believe this text, currently in the results section, represents a valid conclusion in respect to the data presented in the DAP report and is supported by recent publications using ISAC published after the end date of the search strategy described by the evidence review group (i.e. April 2015). These three studies could help define further the role of ISAC, which has been described by the WAO as the "most comprehensive platform currently available (Canonica et al, 2013). A brief description of the studies is given below: • ImmunoCAP ISAC technology has recently been used within two published papers relating to the long-term Manchester Asthma and Allergy Study (MAAS), of which Custovic and Simpson are the lead investigators. These studies provide an early indication that sensitisation to multiple allergen components can appear as clusters associated with potential development of particular clinical outcomes, and that asthma and atopy might be	ImmunoCAP ISAC 112 on management strategies or clinical outcome. Kukkonen et al. 2015 reports data on the accuracy of Ara components (measured using ImmunoCAP ISAC) for determining moderate to severe peanut allergy, as defined by clinical history and SPT. However, the article did not report any comparative accuracy data for ImmunoCAP ISAC versus other testing strategies, or any data on additional clinical information provided by ImmunoCAP ISAC.

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				umbrella terms for specific subtypes of sensitisation. ○ Simpson et al identified a correlation between IgE sensitisation patterns and risk of asthma and hay fever (Simpson et al, J Allergy Clin Immunol 2015; e-pub ahead of print). ○ Custovic et al concluded that longitudinal patterns of sensitisation to allergen components of Timothy grass and dust mite can vary over time and bear different associations with clinical outcomes (Custovic et al, J Allergy Clinical Immunol 2015; e-pub ahead of print). • A separate study of co-sensitisation to peanut allergens revealed that among 6–18 year olds with at least a high suspicion of peanut allergy, Ara h 2 and Ara h 6 sensitisation was associated with severe reactions, whereas specific IgE to Ara h 8 appeared to indicate tolerance or mild sensitisation. The authors concluded that component-resolved diagnostics using ISAC could help reduce the need for oral challenge in peanut allergy (Kukkonen et al, Allergy 2015;70:1239–1245). This should reduce the risk of anaphylaxis	

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				among those with the greatest sensitisation. These three publications are sent, together with this response document, for NICE and the evidence review group to consider them in their evaluation of ISAC to support additional diagnostic insight.	
	13	5	Abstract	*Text in DAR* There was some evidence that ImmunoCAP® ISAC may be useful for discriminating allergens which are structurally similar and are recognised by the same IgE antibody (cross-immunoreactive). Detailed cost analyses suggested that multiplex allergen testing would have to result in a substantial reduction of the proportions of patients receiving sIgE testing and oral food challenge tests in order to be cost saving on the short term. *Thermo Fisher Scientific response:* Thermo Fisher Scientific would like to draw the attention of NICE and of the evidence review group to previously supplied data that is due to be published by Savolainen et al (currently data on file) in support of	The report describes a number of possible roles for multiplex allergen testing and does not imply that replacement for sIgE and/or SPT would be the only possibility. However, cost analysis is a different issue to clinical- or cost-effectiveness analysis. There were insufficient effectiveness data to support a full cost-effectiveness analysis. In order for an intervention to be cost-saving in a cost analysis it is inevitable that the intervention must be considered as a replacement for a more costly alternative.

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				the statements made here. Additionally, based on our position as stated in our response to comment 1, we view ISAC as an addition to SPT and/or IgE testing, not as an alternative. As described below, and supported by numerous experts in the peer-reviewed press (see responses throughout this document), oral food challenge (OFC) will determine if sensitisation is linked with clinical allergy, whereas the presence of IgE is an indicator of atopy or a risk marker for future disease and therefore cannot be taken as an absolute marker of disease without additional clinical information. Further, IgE testing itself has been shown to reduce the need for OFC by 40%–60% (Sampson and HO, J Allergy Clin Immunol 1997;100:444-451; Osterballe et al, J Allergy Clin Immunol 2003;112:196-201). Therefore, we urge NICE and the evidence review group not to consider IgE testing as an avoidable part of the diagnostic procedure for allergen sensitisation and potential associated diseases, but rather, as an essential step in the evidence and insight gathering to understand a patient's full risk profile and treatment needs.	
	14	5	Abstract	*Text in DAR*	We believe that the conclusion, as currently worded, reflects the strength of the available

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				Conclusions No recommendations for service provision can be made based on the analyses included in this report. It is suggested that a consensus-based protocol for the use of multiplex allergen testing be developed. The clinical and cost-effectiveness of the proposed protocol should then be assessed by comparing long-term clinical and quality of life outcomes and resource use in patients managed using the protocol to those managed using a standard diagnostic pathway. *Thermo Fisher Scientific response:* Based on the rationale put forward in our response to comment 2 above and based on our position as stated in the response to comment 1, we ask NICE to consider including the following text (currently in the results section of the abstract), or some modified version, in the conclusions. • The very limited available data indicate that the addition of multiplex allergen testing (ImmunoCAP® ISAC) to standard diagnostic work-up can change clinicians' views on the diagnosis, management and treatment of patients. There is	evidence. The ongoing study may be of interest to future revisions of this guidance.

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				some indication that the use of ImmunoCAP® ISAC testing may be useful in guiding decisions on the discontinuation of restrictive diets, the content of allergen SIT prescriptions, and whether or not patients should receive SIT. Regarding the need for further data to impact on clinical outcomes etc., Thermo Fisher Scientific is in complete agreement with the report's conclusion. The WAO has also identified the need for further studies. As a direct consequence, Thermo Fisher Scientific is working with the scientific community to establish a large, multi-centre, prospective, randomised trial of 2300 patients, including a cohort from the UK. • The primary study objective is the evaluation of the effects on patient management of using ImmunoCAP ISAC during diagnostic work-up of suspected complex asthmatic and/or food allergic patients with multiple symptoms. Outcomes measures to assess the impact on management will include time and cost to perceived accurate diagnosis compared with those of patients managed using the standard diagnostic pathway. • Secondary objectives are: o To evaluate the resource utilisation with	

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				ImmunoCAP ISAC compared with patients managed using standard diagnostic pathway. o To evaluate the amount of actionable items (e.g. change in medication, diet, additional diagnostics or avoidance) with ImmunoCAP ISAC in the management of patients with allergy-related multiple symptom compared to patients managed using standard diagnostic pathway. o To evaluate the clinical effects of component resolved diagnostic (CRD) testing with ImmunoCAP ISAC in the management of patients with allergy-related multiple symptoms (measured by clinical improvement specific to food allergy and/or asthma compared to patients managed using standard diagnostic pathway). o To evaluate patient reported outcomes (PROs) of CRD with ImmunoCAP ISAC in the management of patients with allergy related multiple symptoms (measured by PRO improvement specific to food allergy and/or asthma and with generic	

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				EQ-5D compared with patients managed using standard diagnostic pathway). Data from this trial can help to address the current shortage of information regarding the impact of CRD on clinical outcomes, healthcare costs etc., as stated by the evidence research group.	
	15	17	Assessment of cost effectiveness	*Text in DAR* For skin prick test (SPT), sIgE and the food challenge test these were £62.29, £136.37 and £570.00. *Thermo Fisher Scientific response* The source of costs highlighted and the factors that are included in the total cost per item are unclear. Please can the evidence review group state the source of the figures. In particular, we note that Appendix 7 includes mention that costs include 8 allergen tests per person for SPT and IgE. However, an equivalent number is not stated for OFC. In our experience, for multiple suspected allergies more than one food challenge test is required. It would be useful to understand if there is a potential risk of underestimating the costs of	The test costs are presented in Table 12. The methods to calculate these costs are described in more detail in Appendix 7 (including sources). Please, note that the cost calculations are consistent with NICE clinical guideline 116. This includes the OFC. If anything, we would expect the OFC to be overestimated (based on clinical opinion stating that the costs of implementing the food elimination diet might not be applicable), and not underestimated. This is reflected in the last scenario analysis.

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				diagnosis, particularly when considering patients allergic to 2 or more allergens or with allergies to unknown sources.	
	16	18	1	*Text in DAR* effects on clinical outcomes *Thermo Fisher Scientific response* Per our response to comment 1, Thermo Fisher Scientific proposes that the appraisal is focussed on information and its subsequent effect on treatment, per the WAO consensus statement and the NICE guidance on DAPs, rather than a direct effect on clinical outcomes. We therefore repeat our request that NICE and the evidence research group consider a refocussing of the objectives as described in our response to comment 1.	See response to previous comments. The objectives of the assessment were clearly defined and agreed at the protocol development stage. Objectives cannot be re-defined post-hoc.
	17	19	2.1	*Text in DAR* people with allergy that is difficult to manage *Thermo Fisher Scientific response*	See response to comment 7

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				Thermo Fisher Scientific would like to confirm that the phrase 'difficult to manage' corresponds to the full definition in the scoping document: "people with a combination of at least 2 of the following types of allergy: allergic rhinitis, asthma, IgE-mediated and non-IgE-mediated food allergy and other food allergic syndromes such as eosinophilic oesophagitis." (NICE scoping document, page 5).	
	18	19	2.1	*Text in DAR* IgE antibodies are normally present in very small amounts in the body, but levels are raised in allergic disease *Thermo Fisher Scientific response* We wish to clarify this point and add some additional depth to describe the need to identify specific allergens as well as the interpretation of raised levels of specific IgEs in the context of allergic disease. • We agree that total IgE is detectable at very low levels in the absence of sensitisation. However, levels of specific IgEs are considered to be zero in the absence of sensitisation, or to put it another	We believe that these points are adequately covered by the discussion section of the report. – No response required.

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				way, below the lower detection limit of the assay used (Bousquet et al. Allergy 2008;63:341-346). • Detectable levels of specific IgE is an indicator of sensitisation to the allergen in question. However, raised levels of specific IgEs are not always associated with any physical symptoms or even positive SPTs (Bousquet et al, Allergy 2008;63:341-346). Therefore, it is erroneous to claim a direct causal connection between the IgE test and clinical symptoms without addressing the potential for 'false positive' IgE test results ('clinically irrelevant' results as described by Hamilton and Kleine-Tebbe (Curr Allergy Asthma Rep, 2015; e-pub ahead of print). These authors describe a 'true positive' as 'clinically relevant'. • Hamilton and Kleine-Tebbe, in the article cited in the previous paragraph, state that the "clinical relevance of such an IgE antibody test must be determined by the clinician and not by the test itself." Therefore, we ask the evidence review group to modify its wording to reflect the real nature of IgE testing and results in this context.	

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	19	24	2.2.2	*Text in DAR* 15-20 mins (for SPT) *Thermo Fisher Scientific response* We agree that this is the basic time to perform the test, but consider that the total time, including time to interpret results and time to consult with the patient, will substantially increase the test time, and suggest that the figures are adjusted accordingly. To substantiate our position here, we quote figures reported in Appendix 3.1 (p16) of the NICE guideline 116 (2011) 'Food allergy in children and young people' for SPT: • Nurse time (mins): base case, 30; lower limit, 20; upper limit, 90 • GP time (mins): base case, 10; lower limit, 5; upper limit, 45 Based on these values, the range of 15–20 minutes is at best similar to the lower limit described. We therefore request that the evidence review group reconsiders the estimates of healthcare professional	Consistent with the costing statement and Appendix 3 of the NICE clinical guideline 116, it is indeed assumed that the nurse time is 30 minutes and the GP time is 10 minutes for a SPT with 8 allergens being tested. See appendix 7 of the report for the calculation of the SPT costs.

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				time required for the SPT.	
	20	24	2.2.2	*Text in DAR* 51 allergens per chip (4 chips per slide) 4 patient samples can be analysed at once of 51 allergens each *Thermo Fisher Scientific response* We request that NICE and the evidence review group alter their description of ISAC throughout the document to reflect to purpose of the ISAC chip, based on the following: • ISAC allows the measurement 112 specific IgE components, including those from specific allergen sources and cross-reactive markers.	Section 2.2.1 of the background section, which describes the intervention technologies, includes the statement: 'ImmunoCAP® ISAC 112 is a molecular diagnostic test that can simultaneously test for IgE antibodies to 112 components from 51 allergen sources.' We do not believe that any correction is needed.
	21	24	2.2.2	*Text in DAR* 2. An image scanner is used to identify fluorescently labelled samples, one slide at a time. *Thermo Fisher Scientific response* For full accuracy, we request that NICE and the	The background text is intended to provide a brief overview. We do not believe that the suggested text provides significant additional information.

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				evidence review group state that each slide contains 4 microarrays allowing 4 x 30 microlitre samples per slide to be assayed.	
	22	24	2.2.2	*Text in DAR* 3. Scanned images are analysed *Thermo Fisher Scientific response* For full accuracy, we request that NICE and the evidence review group state that computer-generated reports are automatically produced.	See response to point 21, above.
	23	25	2.2.2	*Text in DAR* No text highlighted it was in the row named "Quantitative results", column named "Skin Prick" *Thermo Fisher Scientific response* We propose, for clarity, that the statement 'no standardised quantitation' be included in this section of the table.	This is a style issue and opinion only – no response needed.
	24	25	2.2.2	*Text in DAR*	See response to point 21, above.

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				Not for use if patient taking anti-histamines Emergency equipment must be available (anti-histamine, adrenaline, hydrocortisone) *Thermo Fisher Scientific response* Thermo Fisher Scientific draws the attention of NICE and the evidence review group to other limitations of the SPT in addition to those highlighted above, including age, skin condition, location on the body, chronobiology, comorbidities, immunotherapy, allergen extract quality and proximity of test allergen to controls or other allergens (Bacharier et al, Allergy 2008;63:5-34; Cox et al, Ann Allergy Asthma Immunol 2008;101:580-592).	
	25	26	2.2.2	*Text in DAR* Table row named “Quantitative results” and column named “Specific IgE” *Thermo Fisher Scientific response* For full accuracy, we request that NICE and the evidence review group include the following:	See response to point 21, above.

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				Quantitative IgE antibody concentration results are reported on a continuous scale, 0–100 kUA/L (reference: ImmunuCAP product information).	
	26	28	2.3	*Text in DAR* tests of clinical reactivity such as skin prick testing or allergen challenge testing, or a combination of these approaches. *Thermo Fisher Scientific response* Thermo Fisher Scientific wishes to draw attention to the descriptions of SPT throughout the report as first-line, a reference standard and a confirmation of clinical disease. • Clinical confirmation: We must reiterate that SPT is not a confirmatory test of allergic disease (however, OFC can be a confirmatory test). SPT, like IgE testing, determines whether detectable IgE sensitisation to specific allergens exists. As numerous authors highlight and demonstrate, SPT and IgE tests can show sensitisation in the absence of allergic disease symptoms as well as negative results in patients exhibiting allergic	We acknowledge the limitations of SPT as a confirmatory test. However, the inclusion criteria for our systematic review were clearly defined in the approved protocol for this assessment: 'Diagnostic accuracy studies will be included only where such studies report the accuracy (sensitivity and specificity) of multiplex allergen testing for the prediction of clinical reactivity, as defined by skin prick tests, allergen challenge tests, or response to immunotherapy; numbers of participants for whom multiplex allergen testing provided additional information will also be recorded.' The point that SPT alone would not be sufficient as a confirmatory test does not affect this assessment, as accuracy studies using SPT in combination with clinical history as a reference standard were included in our systematic review (provided that these studies met all other inclusion criteria). In fact, there were no included studies which

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				symptoms (Bacharier et al, Allergy 2008;63:5-34; Bousquet et al, Allergy 2008;63:341-346; Cox et al, Ann Allergy Asthma Immunol 2008;101:580-592; Hamilton and Kleine-Tebbe, Curr Allergy Asthma Rep 2015; e-pub ahead of print). Authors are clear and consistent that the results of SPT and IgE tests must be interpreted by experienced healthcare professionals in the context of clinical history, and that the results themselves are not inherently diagnostic of allergic disease. • In this context, ISAC (per our position in the response to comment 1 and as demonstrated in the data published by Custovic et al [2015], Sastre et al [2012] and Simpson et al [2015] described in that section) can help to provide additional information regarding specific allergen components and groupings thereof and may help predict sensitivity to certain allergens (e.g. Kukkonen et al, 2015). However, clinical judgement based on history and symptomatology is required for proper interpretation of these sensitisation tests. • Reference standard/first line: Both SPT and IgE are standard methods of detecting IgE sensitisation. SPT is subject to a number of	used SPT alone as a reference standard (see table 7 and appendix 2 table e, in the report). For clarity, we will re-phrase background text as necessary ahead of publication (see response to comment 43, below). With respect to the new 2015 references cited, please see response to comment 12, above.

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				limitations (results affected by age, skin condition, medications such as antihistamines, locations of testing on the body, sun exposure, chronobiology, quality of allergen extract; inherent histamine sensitivity, proximity to other test products on the skin, lack of standardised measures of interpretation) that render interpretation difficult (Cox et al, Ann Allergy Asthma Immunol 208;101:580-592). Thus, SPT by itself cannot be considered a reference standard. This is reinforced by the conclusion by NICE in the 2011 guidance of food allergy in children that SPT and specific IgE tests are similar in diagnostic performance and cost-effectiveness (NICE guidance 116, Food allergy in children and young people, 2011). • Within IgE testing, ImmunoCAP has been considered the gold standard for some time (Bacharier et al. Allergy 2008;63:5-34; Bousquet et al. Allergy 2008;63:341-346; Dolen. Allergy 2003:58:717-723; NIH/NIAID food allergy guideline. J Allergy Clin Immunol 2010;126:S1-S58). It is inherently subject to the detection of both clinically relevant and apparently clinically irrelevant IgE sensitisations (Hamilton and Kleine-	

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				Tebbe, Curr Allergy Asthma Rep 2015; e-pub ahead of print). • Based on the evidence described in our response to comment 1 in this document, it is our position that information gained using ISAC can add additional diagnostic insight to the results of IgE and SPT tests, including 'false' negatives and positives, that may identify cross-sensitisation, potential severity of allergic disease in some individuals and/or the risk of specific allergic disease in others.	
	27	28	2.3.1	*Text in DAR* Unlike IgE antibody testing, skin prick tests and allergen challenge test can provide direct information about clinical reactivity to a given allergen *Thermo Fisher Scientific response* Thermo Fisher Scientific wishes to draw attention to the descriptions of SPT throughout the report as first-line, a reference standard and a confirmation of clinical disease. • Clinical confirmation: We must reiterate that SPT	See response to comment 26, above.

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				is not a confirmatory test of allergic disease (however, OFC can be a confirmatory test). SPT, like IgE testing, determines whether detectable IgE sensitisation to specific allergens exists. As numerous authors highlight and demonstrate, SPT and IgE tests can show sensitisation in the absence of allergic disease symptoms as well as negative results in patients exhibiting allergic symptoms (Bacharier et al, Allergy 2008;63:5-34; Bousquet et al, Allergy 2008;63:341-346; Cox et al, Ann Allergy Asthma Immunol 2008;101:580-592; Hamilton and Kleine-Tebbe, Curr Allergy Asthma Rep 2015; e-pub ahead of print). Authors are clear and consistent that the results of SPT and IgE tests must be interpreted by experienced healthcare professionals in the context of clinical history, and that the results themselves are not inherently diagnostic of allergic disease. • In this context, ISAC (per our position in the response to comment 1 and as demonstrated in the data published by Custovic et al [2015], Sastre et al [2012] and Simpson et al [2015] described in that section) can help to provide additional information regarding specific allergen components and groupings thereof and may help	

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				predict sensitivity to certain allergens (e.g. Kukkonen et al, 2015). However, clinical judgement based on history and symptomatology is required for proper interpretation of these sensitisation tests. • Reference standard/first line: Both SPT and IgE are standard methods of detecting IgE sensitisation. SPT is subject to a number of limitations (results affected by age, skin condition, medications such as antihistamines, locations of testing on the body, sun exposure, chronobiology, quality of allergen extract, inherent histamine sensitivity, proximity to other test products on the skin; lack of standardised measures of interpretation) that render interpretation difficult (Cox et al, Ann Allergy Asthma Immunol 208;101:580-592). Thus, SPT by itself cannot be considered a reference standard. This is reinforced by the conclusion by NICE in the 2011 guidance of food allergy in children that SPT and specific IgE tests are similar in diagnostic performance and cost-effectiveness (NICE guidance 116, Food allergy in children and young people, 2011). • Within IgE testing, ImmunoCAP has been	

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				considered the gold standard for some time (Bacharier et al. Allergy 2008;63:5-34; Bousquet et al. Allergy 2008;63:341-346; Dolen. Allergy 2003:58:717-723; NIH/NIAID food allergy guideline. J Allergy Clin Immunol 2010;126:S1-S58). It is inherently subject to the detection of both clinically relevant and apparently clinically irrelevant IgE sensitisations (Hamilton and Kleine-Tebbe, Curr Allergy Asthma Rep 2015; e-pub ahead of print). • Based on the evidence described in our response to comment 1 in this document, it is our position that information gained using ISAC can add additional diagnostic insight to the results of IgE and SPT tests, including 'false' negatives and positives, that may identify cross-sensitisation, potential severity of allergic disease in some individuals and/or the risk of specific allergic disease in others.	
	28	29	2.3.2	*Text in DAR* SPT results provide evidence of IgE in skin-resident mast cells which may, but does not always, correlate with clinical reactivity.	See response to comment 26, above.

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				Thermo Fisher Scientific response We agree with this statement in the context of responses to comments 17 and 18, and request that previously highlighted statements are reworded accordingly for accuracy and consistency.	
	29	39	3.1.2	*Text in DAR* The inclusion criteria were expanded to allow studies which reported direct comparisons of diagnostic accuracy between sIgE testing and multiplex allergen testing, using skin prick or allergen challenge test as the reference standard *Thermo Fisher Scientific response* Thermo Fisher Scientific wishes to draw attention to the descriptions of SPT throughout the report as first-line, a reference standard and a confirmation of clinical disease. • Clinical confirmation: We must reiterate that SPT is not a confirmatory test of allergic disease (however, OFC can be a confirmatory test). SPT,	We agree that the use of SPT alone as a reference standard represents a further possible weakness in diagnostic accuracy studies. However, this was clearly specified in the agreed protocol. As previously stated (see response to comment 4) we do not believe that diagnostic performance/accuracy data alone can provide sufficient evidence to support the clinical utility of multiplex allergen testing.

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				like IgE testing, determines whether detectable IgE sensitisation to specific allergens exists. As numerous authors highlight and demonstrate, SPT and IgE tests can show sensitisation in the absence of allergic disease symptoms as well as negative results in patients exhibiting allergic symptoms (Bacharier et al, Allergy 2008;63:5-34; Bousquet et al, Allergy 2008;63:341-346; Cox et al, Ann Allergy Asthma Immunol 2008;101:580-592; Hamilton and Kleine-Tebbe, Curr Allergy Asthma Rep 2015; e-pub ahead of print). Authors are clear and consistent that the results of SPT and IgE tests must be interpreted by experienced healthcare professionals in the context of clinical history, and that the results themselves are not inherently diagnostic of allergic disease. • In this context, ISAC (per our position in the response to comment 1 and as demonstrated in the data published by Custovic et al [2015], Sastre et al [2012] and Simpson et al [2015] described in that section) can help to provide additional information regarding specific allergen components and groupings thereof and may help predict sensitivity to certain allergens (e.g. Kukkonen et al, 2015). However, clinical	

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	30	59	3.2.4	*Text in DAR* However, it should be noted that the addition of ImmunoCAP® ISAC also resulted in the identification of large numbers of sensitisations that were not considered to be associated with the anaphylaxis, i.e. large numbers of clinically false positive test results	See response to comment 10.

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				Thermo Fisher Scientific response In the context of our position that adding ISAC to SPT and/or IgE testing can provide additional diagnostic insight, we ask NICE and the evidence review group to consider revising this statement to indicate that other positive results may be reflective of other risks than purely anaphylaxis, i.e. indicative of cross-sensitisation. • For example, Custovic et al (J Allergy Clin Immunol 2015; e-pub ahead of print) identified several classes of level of sensitisation to Timothy grass or mite allergen components using ISAC in a UK birth cohort, based on positive results for individual components of each source (i.e. using the additional information provided by the number of positive results). Levels of sensitisation varied throughout childhood in some cases, particularly for grass allergen components. When the health status of children in each sensitisation group was evaluated, it was found that early sensitisation to grass components was associated with asthma and diminished lung function, whereas late onset	

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				sensitisation was associated with rhinitis. • Studying the same MAAS cohort, clustering of allergen component positive results using data from ISAC identified three component groups (one involving plant protein families, another featuring components of plant, animal and fungal origin, and the third comprising mite allergen components; Simpson et al, J Allergy Clin Immunol 2015; e-pub ahead of print). Sensitisation to the mixed plant/animal/fungal component group was associated with asthma and decreased lung function, whereas sensitisation to the plant components was associated with hay fever. Sensitisation to the components in the mite grouping was associated with both asthma and hay fever. • These results indicate that the extra information provided by ISAC, far from being considered 'false positives', can provide potentially important information regarding risk of allergic disease and cross-sensitisation to other allergen components.	
	31	78	4.1.5	*Text in DAR* expert opinion / the use of expert opinion for key	No response required

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				inputs *Thermo Fisher Scientific response* We wish to draw attention to the following statement in the NICE guidance on the diagnostic assessment programme: “test accuracy may vary based on laboratory differences, the skill and experience of those administering or reading the test, batch and other variations in the materials…” (NICE, 2011). Further, as described by Custovic et al (2013) in the context of skin and IgE tests, “results should not be reported as 'positive' or 'negative'.” Therefore, in the context of establishing the credibility of ISAC, we believe that the use of expert opinion is valid. On the other hand, data for ImmunoCAP technology show consistent levels of performance, reliability and precision over up to 20 years, and it is considered to be the gold standard for IgE testing (Bousquet et al, Allergy 2008;63:341-346). As ISAC is based on ImmunoCAP technology, we believe that the ISAC test will show similar levels of consistency and reliability.	

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	32	94	4.3.1	*Text in DAR* that sIgE testing will always be performed before multiplex allergen testing (if sIgE testing is applicable) *Thermo Fisher Scientific response* Thermo Fisher Scientific acknowledges that in specific cases where ISAC is used after IgE testing (or another test), "multiplex allergen testing would be likely to reduce the number of sIgE tests, by ruling out particular allergens thereby reducing the need for OFC" (DAR, p.94) which is supported by the results of Kukkonen et al (2015 in peanut allergy). However, we would like to draw attention to the opinion of the expert quoted in the report who states that "sIgE testing will always be performed before multiplex allergen testing." We recognise that this might be the individual's perception or preferred usage; however, we respectfully question whether sequential use will **always** be the preferred usage. There are cases (e.g. Sastre et al, 2012; Custovic et al, 2015; Simpson et al, 2015) where ISAC can be used **in parallel** with allergen challenge or IgE testing to provide additional diagnostic information to	Indeed, in the flowchart (Figure 7 in the report) it is assumed that sIgE and multiplex testing are used sequential with sIgE always performed before multiplex allergen testing. We agree that it might be possible to use multiplex and sIgE testing in parallel. However, it is unclear whether this represents UK clinical practice. Therefore, we would prefer to stick to the clinical opinion we received from one of the only identified clinical experts in the UK with experience with multiplex testing.

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				understand level of sensitivity (Custovic et al, 2015), risk of disease (Simpson et al, 2015) or SIT requirement (Sastre et al, 2012). This position is also in line with WAO consensus (Canonica et al, 2013): • to aid the diagnostic process in cases of complex sensitisation (to 2 or more allergens, to differentiate genuine from cross sensitisation); • to estimate the level of severity to potentially avoid challenge testing; • to improve the identification of patients who might require SIT. Consequently, Thermo Fisher Scientific asks NICE and the evidence review committee to consider adding in the parallel usage argument outlined above.	
	33	99	4.3.3	*Text in DAR* difference in time (between 5 and 60 minutes) that was needed to interpret the test results. This also holds true for Microtest testing although the range was smaller (between 5 and 10 minutes).	The sources are provided in Appendix 7 of the report.

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				Thermo Fisher Scientific response Please can the evidence review committee provide the source data to support these statements? The origin of these values is unclear in the current report.	
	34	100	4.3.3	*Text in DAR* Skin prick test £62.28 NICE (2011),88 Curtis (Unit Costs of Health and Social Care 2014)90 *Thermo Fisher Scientific response* We ask NICE and the evidence research group to consider adding more information regarding patient limitations for the SPT and risk of anaphylaxis, both of which could be associated with additional costs that appear not to be captured in the report currently.	The current assessment was limited to short term test costs. Long-term costs and other short-term costs were not included (including costs of any adverse events of testing consistently for any of the tests considered). However, we stress in the recommendations for future research that the adverse events of testing should be considered. Moreover, the limited scope of the present assessment was also mentioned as a limitation. Please also note that the higher SPT costs (e.g. if the anaphylaxis costs are added) do not influence the results (except one of the threshold analyses) since an equal amount of SPT was assumed for all strategies
	35	100	4.3.3	*Text in DAR* OFC test £570.00 NICE (2011),88 Department of Health (NHS reference	Please, note that the cost calculations are consistent with NICE clinical guideline 116. This includes the OFC. If anything, we would expect the OFC to be overestimated (based on clinical opinion stating that the costs of implementing the food elimination diet might

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				costs 2015)91 *Thermo Fisher Scientific response* Per our earlier response to comment 5, when considering total costs, the possibility of multiple OFCs should be considered, as the cost of £570 includes only one allergen test (this appears to be the case in Appendix 7 of the DAR). Additionally, the cost for managing anaphylaxis risk should be evaluated, if available.	not be applicable), and not overestimated. This is reflected in the last scenario analysis. See our previous response regarding the costs of anaphylaxis.
	36	100	4.3.3	*Text in DAR* health state costs for being at risk of allergic reaction *Thermo Fisher Scientific response:* In this case, we suggest that direct costs related to SPT and OFC diagnostics should be included, if available.	No health state costs are presented in the report.
	37	107	5.1.1	*Text in DAR* However, it should be noted that the addition of ImmunoCAP® ISAC also resulted in the identification	See response to comment 10.

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				of large numbers of sensitisations that were not considered to be associated with the anaphylaxis, i.e. large numbers of clinically false positive test results *Thermo Fisher Scientific response* In the context of our position that adding ISAC to SPT and/or IgE testing can provide additional diagnostic insight, we ask NICE and the evidence review group to consider revising this statement to indicate that other positive results may be reflective of other risks than purely anaphylaxis, i.e. indicative of cross-sensitisation. • For example, Custovic et al (J Allergy Clin Immunol 2015; e-pub ahead of print) identified several classes of level of sensitisation to Timothy grass or mite allergen components using ISAC in a UK birth cohort, based on positive results for individual components of each source (i.e. using the additional information provided by the number of positive results). Levels of sensitisation varied throughout childhood in some cases, particularly for grass allergen components. When the health status of children in each sensitisation group was	

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	38	113	5.3.1	*Text in DAR* …analyse 56 allergens and provide… *Thermo Fisher Scientific response:* Per comment 11 above, we wish to highlight that important information regarding the number of allergen components in the ISAC chip is the essential information in this case. We ask NICE and the evidence review group to describe the 112 components, both allergen-specific and cross-reactive markers, and not mention the 51 allergens, which is not relevant in this case.	See response to comment 20.
	39	116	5.3.2	*Text in DAR* it does seem likely that multiplex testing, by ruling out some allergens might avoid confirmatory testing with OFC or SPT *Thermo Fisher Scientific response* Thermo Fisher Scientific wishes to raise two points regarding this statement:	This comment refers to a point made in the discussion section and is opinion only – no response needed.

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				• As described elsewhere in this response document, SPT cannot be considered confirmatory of allergic disease, but only indicates sensitisation to the allergen being tested. The occurrence of false positives (i.e. clinically irrelevant) drives a need for interpretation of the test results in the context of medical history. Therefore, we request the wording of this statement be adjusted to remove the mention of SPT in this context. • We agree that in cases of clear cross-reactivity, unnecessary testing can be avoided. Likewise, ISAC can be used to avoid OFC in severe allergy. For example, in a study of co-sensitization to peanut allergens among 6–18 year olds with at least a high suspicion of peanut allergy, Ara h 2 and Ara h 6 sensitisation was associated with severe reactions, whereas specific IgE to Ara h 8 appeared to indicate tolerance or mild sensitisation. The authors concluded that component-resolved diagnostics using ISAC could reduce the need for oral challenge in peanut allergy (Kukkonen et al, Allergy 2015;70:1239-1245). This should reduce the risk of anaphylaxis among those with greatest sensitisation.	

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				• Finally, we would like to point out that IgE testing itself has been shown to reduce the need for OFC by 40%–60% (Sampson and HO, J Allergy Clin Immunol 1997;100:444-451; Osterballe et al, J Allergy Clin Immunol 2003;112:196-201). Therefore, adding ISAC to IgE testing has the potential for additional reductions on the number of OFCs performed.	
	40	116	5.3.2	*Text in DAR* SPT is a simple, safe and quick test (providing results within 15-20 minutes) and it is often the first-line investigation in allergy. *Thermo Fisher Scientific response* Thermo Fisher Scientific wishes to draw attention to the descriptions of SPT throughout the report as first-line, a reference standard and a confirmation of clinical disease. • Clinical confirmation: We must reiterate that SPT is not a confirmatory test of allergic disease (however, OFC can be a confirmatory test). SPT, like IgE testing, determines whether detectable	See response to comment 26, above.

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				IgE sensitisation to specific allergens exists. As numerous authors highlight and demonstrate, SPT and IgE tests can show sensitisation in the absence of allergic disease symptoms as well as negative results in patients exhibiting allergic symptoms (Bacharier et al, Allergy 2008;63:5-34; Bousquet et al, Allergy 2008;63:341-346; Cox et al, Ann Allergy Asthma Immunol 2008;101:580-592; Hamilton and Kleine-Tebbe, Curr Allergy Asthma Rep 2015; e-pub ahead of print). Authors are clear and consistent that the results of SPT and IgE tests must be interpreted by experienced healthcare professionals in the context of clinical history, and that the results themselves are not inherently diagnostic of allergic disease. • In this context, ISAC (per our position in the response to comment 1 and as demonstrated in the data published by Custovic et al [2015], Sastre et al [2012] and Simpson et al [2015] described in that section) can help to provide additional information regarding specific allergen components and groupings thereof and may help predict sensitivity to certain allergens (e.g. Kukkonen et al, 2015). However, clinical judgement based on history and symptomatology	

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	41	117	6.1	*Text in DAR* From the limited evidence available it appears that the most likely role of multiplex allergen testing would be to replace some or all single sIgE testing *Thermo Fisher Scientific response*	This is just one of the possible roles suggested in the conclusions, which also include tailoring treatment and providing additional information.

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				• Please refer to the response to comment 2 above for our proposal to replace the identified text. • We wish to reiterate that Thermo Fisher Scientific does not seek nor recommend to use ISAC to replace IgE testing nor the other gold standard of allergen sensitisation, the SPT. We believe that the greatest value in including ISAC in the diagnostic process is to provide additional information and insight to aid the physician in the diagnosis and subsequent selection of management protocols, as stated elsewhere in this document.	
	42	117	6.1	*Text in DAR* … these tests have the potential to provide a lot of information in a single step. Although confirmatory testing (SPT or OFC) is still likely to be required, multiplex testing could be used to tailor confirmatory testing to the individual patient and thus reduce the overall testing burden *Thermo Fisher Scientific response*	See response to comment 26, above.

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				Thermo Fisher Scientific wishes to draw attention to the descriptions of SPT throughout the report as first-line, a reference standard and a confirmation of clinical disease. • Clinical confirmation: We must reiterate that SPT is not a confirmatory test of allergic disease (however, OFC can be a confirmatory test). SPT, like IgE testing, determines whether detectable IgE sensitisation to specific allergens exists. As numerous authors highlight and demonstrate, SPT and IgE tests can show sensitisation in the absence of allergic disease symptoms as well as negative results in patients exhibiting allergic symptoms (Bacharier et al, Allergy 2008;63:5-34; Bousquet et al, Allergy 2008;63:341-346; Cox et al, Ann Allergy Asthma Immunol 2008;101:580-592; Hamilton and Kleine-Tebbe, Curr Allergy Asthma Rep 2015; e-pub ahead of print). Authors are clear and consistent that the results of SPT and IgE tests must be interpreted by experienced healthcare professionals in the context of clinical history, and that the results themselves are not inherently diagnostic of allergic disease. • In this context, ISAC (per our position in the	

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				response to comment 1 and as demonstrated in the data published by Custovic et al [2015], Sastre et al [2012] and Simpson et al [2015] described in that section) can help to provide additional information regarding specific allergen components and groupings thereof and may help predict sensitivity to certain allergens (e.g. Kukkonen et al, 2015). However, clinical judgement based on history and symptomatology is required for proper interpretation of these sensitisation tests. • Reference standard/first line: Both SPT and IgE are standard methods of detecting IgE sensitisation. SPT is subject to a number of limitations (results affected by age, skin condition, medications such as antihistamines, locations of testing on the body, sun exposure, chronobiology, quality of allergen extract, inherent histamine sensitivity, proximity to other test products on the skin, lack of standardised measures of interpretation) that render interpretation difficult (Cox et al, Ann Allergy Asthma Immunol 208;101:580-592). Thus, SPT by itself cannot be considered a reference standard. This is reinforced by the conclusion by NICE in the 2011	

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				guidance of food allergy in children that SPT and specific IgE tests are similar in diagnostic performance and cost-effectiveness (NICE guidance 116, Food allergy in children and young people, 2011). • Within IgE testing, ImmunoCAP has been considered the gold standard for some time (Bacharier et al. Allergy 2008;63:5-34; Bousquet et al. Allergy 2008;63:341-346; Dolen. Allergy 2003:58:717-723; NIH/NIAID food allergy guideline. J Allergy Clin Immunol 2010;126:S1-S58). It is inherently subject to the detection of both clinically relevant and apparently clinically irrelevant IgE sensitisations (Hamilton and Kleine-Tebbe, Curr Allergy Asthma Rep 2015; e-pub ahead of print). • Based on the evidence described in our response to comment 1 in this document, it is our position that information gained using ISAC can add additional diagnostic insight to the results of IgE and SPT tests, including 'false' negatives and positives, that may identify cross-sensitisation, potential severity of allergic disease in some individuals and/or the risk of specific allergic	

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				disease in others.	
The Royal College of Nursing	43	29	2.3.2	The first sentence implies that skin prick tests (SPTs) diagnose IgE mediated allergic disease. They are used to assist in the diagnosis…. History is SO important in diagnosing IgE mediated allergic disease.	We agree with this point and will make changes to the background text ahead of publication.
	44	General	General comment	Our reviewer considered the document a very complex piece to read, but agrees with the conclusions. Note that ImmunoCAP ISAC or Microtest would not be used first line, but could help in the more complicated patients that are seen. The end point is that parents want to be confident that their child can eat a variety of foods safely.	No response required.
NHS Professional 1	45	14	Scientific summary	There are major practical difficulties in assessing the effects on clinical outcomes of adding multiplex allergen tests to the investigation of people with difficult to manage allergic disease. These patients are for resource reasons not followed up in many clinical allergy services, which are in the UK forced because of lack of funding to perform a diagnostic role only, make recommendations to general practitioners to manage the patients in primary care, and not follow up the patients because of the political focus on waiting	No response required

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				times for new patient appointments. Following up such patients in order to assess carefully the effects of these investigations and their detailed impact on actual clinical outcomes is not realistic in most NHS services, as there is a lack of capacity to see the patients back in the outpatient clinics for the detailed follow-up required. Such appointments would increase the waiting time for the massive number of routine referrals the services get, and this would have a politically unacceptable impact on new patient waiting times.	
	46	15	Results	For the above reason it is hardly surprising that no studies were identified of people with difficult to manage allergic disease in the UK, and that no studies were identified which investigated clinical outcomes. In summary, when the massive demand for allergy services and the pitiful small capacity are pitted against the perceived need for rigorous studies, it is hardly surprising that (in the UK a least) wrestling with the alligators takes precedence over draining the swamp.	We acknowledge the potential conflict between the 'ideal' study and what is practically possible. However, some evidence of a clinical effect of testing is needed. Detailed recommendations for future research are a matter for discussion by the committee.
	47	58/59	3.2.4	The summary in this section states that 'The results of studies in this section provide some indication that the addition of ImmunoCAP® ISAC to standard diagnostic work-up can change the clinicians' views on the diagnosis, management and treatment of patients. There was some indication that the use of ImmunoCAP® ISAC testing may guide decisions on	See response to point 46, above

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				the discontinuation of restrictive diets, the content of SIT prescriptions, and whether or not patients should receive SIT.' In the field of clinical allergy diagnosis, diagnostic tests play a crucial role in confirming diagnoses that are suspected on clinical grounds (predominantly from the patient's history, and sometimes guided by probability). They occasionally provide extra, surrounding information that helps to place that diagnosis in its overall immunological/allergic context. In Clinical Allergy, in the great majority of patients, making the correct, appropriately finessed diagnosis, is in itself the major intervention that the doctor makes on behalf of the patient. All aspects of the management of clinical allergy automatically follow on from the correct diagnosis, and depend upon the severity of the symptoms that the patient suffers as a consequence of that allergy. Thus any test that 'can change the clinicians views on the diagnosis and management and treatment of patients' is potentially of profound value in that patients clinical management, and will thus have a comments rich impact on the long-term outcome of the patient. I did not have the impression that perceived effects on clinical outcomes for patients played such a seemingly important role in the deliberations of NICE on the use	

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				of different combinations of diagnostic tests in the analogous field of diagnostic tests for coeliac disease. I am surprised that NICE should seem to wish to set the bar so much higher in this evolving area that addresses the allergy pandemic of increasingly prevalent and increasingly severe allergy than in the extremely well mapped and in comparison rather clinically static area of coeliac disease. It appears as if NICE may not fully appreciate that the most valuable service patients with allergy require at present to secure their clinical interests is to make the correct clinical diagnosis in nuanced detail.	
	48	59	3.2.4	The summary in this section concludes that 'However, it should be noted that the addition of ImmunoCAP® ISAC also resulted in the identification of large numbers of sensitisations that were not considered to be associated with the anaphylaxis, i.e. large numbers of clinically false positive test results.' This is not a disadvantage - the demonstration of hitherto unidentified sensitisations by ISAC is extremely relevant in patients who have idiopathic anaphylaxis. It alerts the clinician to the possibility that allergens to which the patient is sensitised may precipitate these severe symptoms. The demonstration of sensitisations of uncertain importance in this group of patients is precisely that - it remains of uncertain clinical importance. It is not an informational disadvantage or flawed information.	See response to comment 10.

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	49	107	5.1.1	The statement 'The results of the very limited number of available studies provide some indication that the addition of multiplex allergen testing (ImmunoCAP® ISAC) to standard diagnostic work-up can change the clinicians' views on the diagnosis, management and treatment of patients' constitutes clear recognition of the value of ISAC in altering or nuancing the clinical diagnosis. Information on clinical outcomes is not available for the reasons given earlier.	No response required.
NHS Professional 2	50		General	In my opinion, the conclusions by the evidence review group that no recommendations for service provision can currently be made, and the suggestion that a consensus-based protocol for the use of multiplex allergen testing should be developed be developed are an excellent reflection of the currently available evidence. I would like to add the following, which I believe has not been captured in the report: 1. It is now clear that asthma (and most other allergic conditions such as rhinitis or anaphylaxis) are not single diseases, but umbrella diagnoses which comprises multiple diseases with distinct mechanisms, and likely completely different response to available treatments. 2. These asthma (and atopy) subtypes (clusters /	No response required.

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				classes / phenotypes) can currently be identified only by using statistical inference on longitudinal data, and differentiation at any single cross-sectional point is not as yet possible. By extension, we are not practicing stratified or personalised medicine. 3. The crucial step to deliver stratified medicine in clinical practice is the discovery of biomarkers to help early identification of such subgroups of disease, which would have practical value for clinicians. 4. Patterns of IgE responses to allergen components in multiplex chips such as ImmunoCAP ISAC may offer important additional information to enable identification of subtypes of allergic diseases and help better ascertain the future risk (e.g. of exacerbations among asthmatic patients), facilitating more personalized approach to management (in line with GINA guidelines). 5. Furthermore, whilst most patients with asthma are sensitized to aeroallergens, only a minority of sensitized individuals are symptomatic, suggesting the existence of underlying efficient anti-inflammatory control mechanisms, and patterns of the response on multiplex chips may help differentiate “benign” from “pathologic” sensitization.	

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				Really excellent work by the by the evidence review group.	