Consensus for genes to be included on cancer panel tests offered by UK Genetics Services: Guidelines of the UK Cancer Genetics Group

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Abstract

Genetic testing for hereditary cancer predisposition has evolved rapidly in recent years with the discovery of new genes, but there is much debate over the clinical utility of testing genes for which there is currently limited data regarding the degree of associated cancer risk. To address the discrepancies that have arisen in the provision of these tests across the UK, the UK Cancer Genetics Group (UK-CGG), facilitated a one-day workshop with representation

from the majority of NHS Clinical Genetics Services. Using a pre-workshop survey followed by focused discussion of genes without prior majority agreement for inclusion, we achieved consensus for panels of cancer genes with sufficient evidence for clinical utility, to be adopted by all NHS Genetics Services. To support consistency in the delivery of these tests and advice given to families across the country, we also developed management proposals for individuals who are found to have pathogenic mutations in these genes. However, we fully acknowledge that the decision regarding what test is most appropriate for an individual family rests with the clinician, and will depend on factors including specific phenotypic features and the family structure.

Background

NHS Clinical Genetics Services have in recent years taken advantage of the discovery of new genes and emerging evidence for associated cancer predisposition to carry out more extensive genetic testing via cancer gene panels, aiming to provide information and tailored management for more families with a hereditary cancer predisposition. However, there is much debate over the utility of testing genes for which there exists limited data regarding impact on cancer risk[1], and the gradual evolution of these panels has led to discrepancies in the genes tested by different laboratories. This has resulted in differences between what is offered to patients, as well as difficulty in managing families where relatives are located in different parts of the country. For example, a relative may find that testing for the gene identified in their family is not offered in their region, or may be given different advice about risk management from that given to a relative with the same genetic variant.

To address this, the UK Cancer Genetics Group (UK-CGG), supported by the UK Genetic Testing Network (UKGTN), facilitated a one-day workshop to achieve consensus for panels of cancer genes with clear clinical utility, to be adopted by all NHS Genetics Services. In addition, consensus guidelines for the management of individuals with pathogenic variants in these genes were subsequently developed.

Methods

Scope

The workshop focused on panels of genes for breast cancer, ovarian cancer, colorectal cancer and polyposis. These were selected as the most commonly used panels, and also those with the largest discrepancies regarding inclusion of genes.

Participants

Invitations were sent to the Lead Cancer Clinicians at each of the 24 UK Genetics Services, and if unable to attend they were given the option to send a colleague in their place. All but two services were represented at the workshop. Also represented were Clinical Scientists from NHS Genetics Laboratories currently offering cancer panel tests, Genetic Counsellors with a specialist interest in cancer genetics, and representatives from UKGTN, UK-CGG, and Genomics England.

Pre-workshop survey

Lists of potential genes were compiled from panel tests currently on offer at both NHS and private laboratories. Workshop participants were surveyed for their opinions on the inclusion of each gene prior to the workshop, in order to focus discussion on genes where inclusion was most contentious. Genes were deemed to have majority agreement if >75% of participants said they should be included.

Presentation of evidence for and against inclusion of genes

Based on their survey responses, workshop participants were asked to present either for or against the inclusion of genes with <75% prior agreement. Those presenting in favour of inclusion were also asked to present management proposals for families where a pathogenic variant was identified (see supplementary information 1).

Discussion groups

Participants were divided into three groups to discuss breast cancer, epithelial ovarian cancer, and colorectal cancer/polyposis gene panels. Each group formulated a proposed panel based on the evidence presented, which was then presented to the full workshop, openly discussed and agreed. The focus of discussion was on the clinical utility of identifying

pathogenic variants in each gene, but practical considerations of testing specific genes were also taken into account.

Meeting report

The agreed cancer panels were circulated to all attendees following the workshop, and were presented at the UK-CGG Spring Meeting 2017 for further comment. The manuscript was also circulated to the attendees. It should be noted that this report is a summary of the workshop, and therefore does not necessarily represent the opinions of individual attendees or Genetics Services.

Results & Discussion

Pre-workshop survey

Responses were received from 78% (25/32) of the clinicians and clinical scientists who were invited to complete the survey (see supplementary information 2). The survey asked separate questions about inclusion of genes on breast cancer, ovarian cancer, colorectal cancer and polyposis panels. The results for colorectal cancer and polyposis panels overlapped completely, reflecting the recognised overlap in phenotypes[2] and indicating that this should be established as a single panel.

Genes with majority agreement (>75%) for each panel were as follows:

Breast cancer: *BRCA1, BRCA2, PALB2, PTEN, STK11, TP53*

Ovarian cancer: *BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, RAD51C, RAD51D*

Colorectal cancer/polyposis: *APC, MUTYH, SMAD4, BMPR1A, MLH1, MSH2, MSH6, PMS2, EPCAM* (deletion of exons 8-9), *POLE, POLD1, STK11*

Genes included or excluded following presentation of evidence and discussion

Breast cancer panel

It was agreed to include *ATM* and *CHEK2*, which both confer a moderately increased risk of breast cancer[1 3], but concerns about the interpretation of results for these genes led to the

recommendation that only truncating variants should be reported[4], in addition to *ATM* c.7217T>G p.(Val2424Gly) which is recognised as conferring a higher risk of breast cancer[5]. Insufficient evidence was found for a significant risk of breast cancer associated with *NBN*[6], *BRIP1*[7] or *BARD1*[6], so these were excluded from the panel. *CDH1* was also excluded due to its relevance only in cases of lobular breast cancer, and the considerable difficulty presented by interpreting variants in families with no history of lobular breast cancer or diffuse gastric cancer[8]. However, testing for *CDH1* should be available for relevant cases and offered according the current guidelines[9]. It was noted that the inclusion of single nucleotide polymorphisms (SNPs) associated with breast cancer risk[10] will need to be considered in future, but will be more relevant to predicting risk in unaffected individuals rather than genetic testing of individuals with cancer[11].

Ovarian cancer panel

It was agreed to include *BRIP1*, which confers sufficient risk of ovarian cancer such that prophylactic bilateral salpingo-oophorectomy is considered[12]. Insufficient evidence was found for a significant risk of ovarian cancer associated with the *EPCAM* deletion[13], *TP53*[14], and also *PMS2* which originally had majority agreement in the survey, but was excluded when new data was taken into account[15]. *STK11* was also excluded since mutations are associated only with a rare type of ovarian cancer - sex cord tumours with annular tubules - so testing on a gene panel primarily intended for individuals with epithelial ovarian cancer was not considered appropriate. For a review of genes to consider in rare non-epithelial ovarian neoplasms, see Foulkes *et al*, 2016[16].

Colorectal cancer / polyposis panel

Only two genes did not secure majority agreement for inclusion - *GREM1* (upstream duplication) and *NTHL1* - although the survey results suggested respondents were unsure about these genes rather than that they disagreed with their inclusion. Following discussion it was agreed that both these genes could be included, but this should be optional since the

GREM1 upstream duplication has to date only been reported in individuals with Ashkenazi Jewish ancestry, and the frequency of pathogenic mutations in *NTHL1* is low[17].

A summary of the agreed panels is given in Table 1.

Table 1: Agreed panels

Breast cancer	**Ovarian cancer**	**Colorectal cancer / polyposis**
*ATM**	*BRCA1*	*APC*
BRCA1	*BRCA2*	*BMPR1A*
BRCA2	*BRIP1*	*EPCAM* (del exons 8-9)
*CHEK2***	*MLH1*	*GREM1* (upstream dup)*
PALB2	*MSH2*	*MLH1*
PTEN	*MSH6*	*MSH2*
STK11	*RAD51C*	*MSH6*
TP53	*RAD51D*	*MUTYH*
		*NTHL1**
* truncating variants plus *ATM* c.7271T>G, p.(Val2424Gly)		*PMS2*
		POLE
** truncating variants		*POLD1*
		PTEN
		SMAD4
		STK11
		*optional

Expected standard of analysis

It is expected that analysis will include sequencing of the coding region and intron/exon boundaries of each gene, except for *EPCAM* and *GREM1,* where only the common del/dup need be tested for. It is expected that copy number analysis to detect exonic deletions and duplications from sequencing data will be possible in the near future, but in the meantime this analysis should be carried out separately for the key genes *BRCA1*, *BRCA2*, *APC*, *MLH1*, *MSH2*, *MSH6* and *PMS2*. For other genes, copy number analysis can be added where possible, but if not included this must be made clear on the report.

Management proposals

One of the key aims of this consultation was to improve consistency of service delivery across the UK, and it was recognised that this extends to the management of individuals found to have pathogenic variants, as well as which genes are included on each panel. Although the level of evidence for some of the included genes makes the establishment of firm guidelines challenging, it was agreed that pragmatic management proposals would be of benefit to the UK cancer genetics community. These are summarised in Table 2.

Table 2

Breast cancer genes		
Gene	**Breast cancer risk management**	**References**
ATM * §	12-18 monthly mammography from 40-50 depending on family history, then NHSBSP For c.7271T>G consider *BRCA*-equivalent	Ataxia Telangiectasia in Children: Guidance on Diagnosis and Clinical Care[18] Protocols for the surveillance of women at higher risk of developing breast cancer, Public Health England 2013[19]
BRCA1	As per national guidelines	NICE CG164[20]
BRCA2	As per national guidelines	NICE CG164[20]
CHEK2 + §	12-monthly mammography from 40-50, then NHSBSP For homozygotes consider *BRCA*-equivalent	Tung *et al* 2016[21]
PALB2 §	Consider *BRCA*-equivalent	Tung *et al* 2016[21]
PTEN ++	Consider *BRCA*-equivalent	UK-CGG Guidelines for management of tumour risk in PTEN hamartoma syndrome 2017[22]
STK11	Consider *BRCA*-equivalent	Beggs *et al,* 2010[23]
TP53	As per national guidelines	NICE CG164[20]

* The Ataxia Telangiectasia guidelines recommend 18-monthly mammography, but where *ATM* pathogenic variants are identified in the context of a significant family history of breast cancer it is reasonable to offer annual mammography, bringing this into line with *CHEK2* mutation carriers who have a similar risk. The guidelines do not give specific recommendations for the c.7271T>G variant so this is pragmatic, based on the evidence indicating this variant confers a much higher risk.

[+] These recommendations include mammography and/or breast MRI. Given that the risk for *CHEK2* c.1100delC is well defined it is reasonable to offer mammography rather than MRI. There is much weaker evidence for other *CHEK2* variants but it seems reasonable to use the same protocol for these until further data emerge.

[++] These recommendations include mammography and/or breast MRI. As there is good evidence that the *PALB2* risk is influenced by other factors such as family history it would be reasonable to offer *BRCA*-equivalent surveillance to those women ascertained via family history clinics (where there is a strong family history) but to consider less intense surveillance in those women with no significant family history (e.g. an incidental finding).

[§] For *ATM*, *CHEK2* and *PALB2* consider using BOADICEA to guide risk management[24]

Ovarian cancer genes		
Gene	**Ovarian cancer risk management**	**References**
BRCA1	As per national guidelines	NICE CG164[20]
BRCA2	As per national guidelines	NICE CG164[20]
BRIP1	Consider RRSO at 45–50 y (and once family complete)	Tung *et al* 2016[21]
MLH1	Consider TAH and BSO from 40 y (and once family complete)	Vasen *et al* 2013[25], Daly *et al* 2017[26]
MSH2	Consider TAH and BSO from 40 y (and once family complete)	Vasen *et al* 2013[25], Daly *et al* 2017[26]

MSH6	Consider TAH and BSO from 40 y (and once family complete)	Vasen *et al* 2013[25], Daly *et al* 2017[26]
RAD51C	Consider RRSO at 45–50 y (and once family complete)	Tung *et al* 2016[21], Daly *et al* 2017[26]
RAD51D	Consider RRSO at 45–50 y (and once family complete)	Tung *et al* 2016[21], Daly *et al* 2017[26]

Colorectal cancer / polyposis genes		
Syndrome	**Cancer risk management**	**References**
Lynch syndrome Adenomatous polyposis syndromes Peutz Jeghers syndrome Juvenile polyposis syndrome PTEN-hamartomatous tumour syndromes	See International and European guidance as advised by InSiGHT, plus UK guidance on endoscopic colorectal surveillance issued by the British Society of Gastroenterology (due for revision). Guidance on management of Lynch syndrome should be interpreted in the light of gene, gender, age, previous cancer history, as shown by the *Prospective Lynch Syndrome Database* at http://www.lscarisk.org/ The reference databases for interpretation of variants in *MSH2, MLH1, MSH6, PMS2, EPCAM, APC, MUTYH, POLD1, POLE,* and *STK11*, are provided at http://www.insight-database.org/genes	As listed under individual condition headings at:- https://www.insight-group.org/ including:- Vasen *et al* 2008[27] Cairns *et al* 2010[28] Vasen *et al* 2013[25] Møller *et al* 2017[15 29]

Conclusion

Consensus was achieved at the workshop for genes to be included on panel tests for breast cancer, ovarian cancer and colorectal cancer/polyposis. Clinical entry points and testing criteria have not been addressed here since these are currently being developed by NHS

England. It was recognised that when resources are limited there is a tension between investing in panel tests as opposed to testing a smaller number of genes with wider testing criteria. However, the cost of panel testing is dropping rapidly so that in the near future it will likely become more efficient to carry out panel testing on all patients with selective analysis of genes according to testing indication. From a technical point of view, this will be most expedient when panel tests can reliably detect all large (exonic) deletions and duplications as well as sequence variants. It was also recognised that access to and funding for panel tests currently varies across the UK, but it is hoped that one of the outcomes of this consultation will be improved consistency, providing centres with a standard of testing to work towards. However, this aim for consistency is not intended to override a clinician's choice to target specific genes they consider most relevant to a particular family rather than offering a gene panel in every case.

One factor clinicians will take into account is that testing a larger number of genes will result in finding more variants of uncertain significance, which carries a cost in the time spent interpreting and explaining the results, and can leave families with more questions than answers. It is essential that these are collated centrally so that a shared understanding of their significance can be reached more rapidly and consistent information is conveyed to families. It is because of the current challenges in interpreting variants of uncertain significance that at present we have recommended the reporting of only truncating variants in *ATM* and *CHEK2*. However, as these genes become better understood it will no doubt emerge that some missense variants also confer an increased risk of breast cancer, and it is possible that some could be higher penetrance alleles similar to *ATM* c.7271T>G.

Another factor is that particularly in breast cancer families, finding a pathogenic variant in a moderate risk gene in the context of a high risk family history does not always aid clinical management, since the variant cannot be assumed to account for all of the genetic risk in the family. Hence offering testing to unaffected close relatives may not be informative in

helping to advise them about their level of risk and guide decision-making around risk management. However, these variants can be used to identify more distantly related individuals (e.g. those related via intervening unaffected women) who are at moderately increased risk and would not have previously been eligible for additional breast screening. Therefore the decision about whether to offer panel testing will often depend on the family structure and whether there are unaffected individuals to whom the information will be relevant.

It is important to note that this is a rapidly evolving field, and these recommendations will need to be revisited as further evidence emerges for inherited cancer risk. We plan to review the gene lists annually, and any updates will be posted on the UK-CGG website (http://www.ukcgg.org). In particular, the advent of routine tumour sequencing in cancer diagnosis and the move to whole genome sequencing and interrogation of virtual panels will change the contexts and capabilities of germline panel testing. As the technological barriers in sequencing are largely overcome, the importance of testing genes only where there is rigorous clinical evidence will become ever more critical.

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Contributorship statement

AT developed and administered the pre-workshop survey, and analysed the data

AT and AB organised and chaired the workshop

MT, LS, IMF, HH & CT developed management proposals

AT drafted the manuscript

AB, MT, LS, IMF, HH & CT reviewed and critically revised the manuscript

AT, AB, MT, LS, IMF, HH & CT approved the final version for publication

Competing interests

The authors declare no competing interests.

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