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 are 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 facilitated a 1-day workshop with representation from the majority of National Health Service (NHS) clinical genetics services. Using a preworkshop 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
National Health Service (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 exist 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 1-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.

Preworkshop 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 online 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 AND DISCUSSION

Preworkshop survey
Responses were received from 78% (25/32) of the clinicians and clinical scientists who were invited to complete the survey (see online 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 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.

**Table 1**

<table>
<thead>
<tr>
<th>Agreed panels</th>
<th>Breast cancer</th>
<th>Ovarian cancer</th>
<th>Colorectal cancer/polyposis</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM*</td>
<td>BRCA1</td>
<td>BRCA2</td>
<td>APC</td>
</tr>
<tr>
<td>BRCA2</td>
<td>BRCA2</td>
<td>BRCA2</td>
<td>BMPR1A</td>
</tr>
<tr>
<td>BRCA2</td>
<td>BRIP1</td>
<td>EPCAM (del exons 8–9)</td>
<td></td>
</tr>
<tr>
<td>CHEK2†</td>
<td>MLH1</td>
<td>GREM1 (upstream dup)‡</td>
<td></td>
</tr>
<tr>
<td>PALB2</td>
<td>MSH2</td>
<td>MLH1</td>
<td></td>
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<tr>
<td>PTEN</td>
<td>MSH2</td>
<td>MSH2</td>
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<tr>
<td>STK11°</td>
<td>RAD51C</td>
<td>MSH6</td>
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<tr>
<td>TP53°</td>
<td>RAD51D</td>
<td>MSH6</td>
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*Truncating variants plus ATM c.7271T>G, p.(Val2424Gly).
†Truncating variants.
‡Optional.

**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, but concerns about the interpretation of results for these genes led to the recommendation that only truncating variants should be reported, in addition to ATM c.7217T>G, p.(Val2424Gly), which is recognised as conferring a higher risk of breast cancer. Insufficient evidence was found for a significant risk of ovarian cancer associated with the EPCAM deletion, and also PMS2, which originally had majority agreement in the survey, but was excluded when new data were taken into account. 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.

**Ovarian cancer panel**
It was agreed to include BRIP1, which confers sufficient risk of ovarian cancer such that prophylactic bilateral salpingo-oophorectomy is considered. Insufficient evidence was found for a significant risk of ovarian cancer associated with the EPCAM deletion, and also PMS2, which originally had majority agreement in the survey, but was excluded when new data were taken into account. 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.

**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.

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

**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.

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 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.
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 risks 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 (eg, 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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Contributors
Dr Adam developed and administered the preworkshop survey and analysed the data. AT and AFB organised and chaired the workshop. MT, LS, IMF, HH and CT developed management proposals, AT drafted the manuscript, AFB, MT, LS, IMF, HH and CT reviewed and critically revised the manuscript. AT, AFB, MT, LS, IMF and HH approved the final version for publication.

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Competing interests
None declared.

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REFERENCES
Position statement


