CLINICAL GUIDELINES

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[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 to the current guidelines.[9] It was noted that the inclusion of 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 were 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*.[16]

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‡
		PMS2
		POLE
		POLD1
		PTEN
		SMAD4
		STK11

*Truncating variants plus *ATM* c.7271T>G, p.(Val2424Gly).
†Truncating variants.
‡Optional.

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.

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

Table 2 Management proposals.

Breast cancer genes		
Gene	**Breast cancer risk management**	**References**
*ATM**†	12–18 monthly mammography from 40 to 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[19]
BRCA1	As per national guidelines	NICE CG164[20]
BRCA2	As per national guidelines	NICE CG164[20]
CHEK2†‡	12-monthly mammography from 40 to 50, then NHSBSP For homozygotes consider *BRCA*-equivalent	Tung *et al*[21]
PALB2†	Consider *BRCA*-equivalent	Tung *et al*[21]
PTEN§	Consider *BRCA*-equivalent	UK-CGG guidelines for management of tumour risk in PTEN hamartoma syndrome[22]
STK11	Consider *BRCA*-equivalent	Beggs *et al*[23]
TP53	As per national guidelines	NICE CG164[20]
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 BSO at 45–50 years (and once family complete)	Tung *et al*[21]
MLH1	Consider TAH and BSO from 40 years (and once family complete)	Vasen *et al*[25] and Daly *et al*[26]
MSH2	Consider TAH and BSO from 40 years (and once family complete)	Vasen *et al*[25] and Daly *et al*[26]
MSH6	Consider TAH and BSO from 40 years (and once family complete)	Vasen *et al*[25] and Daly *et al*[26]
RAD51C	Consider BSO at 45–50 years (and once family complete)	Tung *et al*[21] and Daly *et al*[26]
RAD51D	Consider BSO at 45–50 years (and once family complete)	Tung *et al*[21] and Daly *et al*[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 and 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 the following: Vasen *et al*[27] Cairns *et al*[28] Vasen *et al*[25] Møller *et al*[15 29]

*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.
†For *ATM*, *CHEK2* and *PALB2* consider using BOADICEA to guide risk management.[24]
‡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 (eg, an incidental finding).
BOADICEA, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; BSO, bilateral salpingo-oophorectomy; NHSBSP, National Health Service Breast Screening Programme; NICE, National Institute for Health and Care Excellence; TAH, total abdominal hysterectomy; UK-CGG, UK Cancer Genetics Group.

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 was also recognised that access to and funding for panel tests currently vary 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 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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REFERENCES

1 Easton DF, Pharoah PD, Antoniou AC, Tischkowitz M, Tavtigian SV, Nathanson KL, Devilee P, Meindl A, Couch FJ, Southey M, Goldgar DE, Evans DG, Chenevix-Trench G, Rahman N, Robson M, Domchek SM, Foulkes WD. Gene-panel sequencing and the prediction of breast-cancer risk. *N Engl J Med* 2015;372:2243–57.
2 Rohlin A, Rambech E, Kvist A, Törngren T, Eiengård F, Lundstam U, Zagoras T, Gebre-Medhin S, Borg Å, Björk J, Nilbert M, Nordling M. Expanding the genotype-phenotype spectrum in hereditary colorectal cancer by gene panel testing. *Fam Cancer* 2017;16:195–203.
3 Couch FJ, Shimelis H, Hu C, Hart SN, Polley EC, Na J, Hallberg E, Moore R, Thomas A, Lilyquist J, Feng B, McFarland R, Pesaran T, Huether R, LaDuca H, Chao EC, Goldgar DE, Dolinsky JS. Associations between cancer predisposition testing panel genes and breast cancer. *JAMA Oncol* 2017;3:1190.
4 Young EL, Feng BJ, Stark AW, Damiola F, Durand G, Forey N, Francy TC, Gammon A, Kohlmann WK, Kaphingst KA, McKay-Chopin S, Nguyen-Dumont T, Oliver J, Paquette AM, Pertesi M, Robinot N, Rosenthal JS, Vallee M, Voegele C, Hopper JL, Southey MC, Andrulis IL, John EM, Hashibe M, Gertz J, Le Calvez-Kelm F, Lesueur F, Goldgar DE, Tavtigian SV. Breast Cancer Family Registry. Multigene testing of moderate-risk genes: be mindful of the missense. *J Med Genet* 2016;53:366–76.
5 Goldgar DE, Healey S, Dowty JG, Da Silva L, Chen X, Spurdle AB, Terry MB, Daly MJ, Buys SM, Southey MC, Andrulis I, John EM, Khanna KK, Hopper JL, Oefner PJ, Lakhani S, Chenevix-Trench G. BCFR kConFab. Rare variants in the ATM gene and risk of breast cancer. *Breast Cancer Res* 2011;13:R73.

6 Li J, Meeks H, Feng BJ, Healey S, Thorne H, Makunin I, Ellis J, Campbell I, Southey M, Mitchell G, Clouston D, Kirk J, Goldgar D, Chenevix-Trench G. kConFab Investigators. Targeted massively parallel sequencing of a panel of putative breast cancer susceptibility genes in a large cohort of multiple-case breast and ovarian cancer families. *J Med Genet* 2016;53:34–42.
7 Easton DF, Lesueur F, Decker B, Michailidou K, Li J, Allen J, Luccarini C, Pooley KA, Shah M, Bolla MK, Wang Q, Dennis J, Ahmad J, Thompson ER, Damiola F, Pertesi M, Voegele C, Mebirouk N, Robinot N, Durand G, Forey N, Luben RN, Ahmed S, Aittomäki K, Anton-Culver H, Arndt V, Baynes C, Beckman MW, Benitez J, Van Den Berg D, Blot WJ, Bogdanova NV, Bojesen SE, Brenner H, Chang-Claude J, Chia KS, Choi JY, Conroy DM, Cox A, Cross SS, Czene K, Darabi H, Devilee P, Eriksson M, Fasching PA, Figueroa J, Flyger H, Fostira F, García-Closas M, Giles GG, Glendon G, González-Neira A, Guénel P, Haiman CA, Hall P, Hart SN, Hartman M, Hooning MJ, Hsiung CN, Ito H, Jakubowska A, James PA, John EM, Johnson N, Jones M, Kabisch M, Kang D, Kosma VM, Kristensen V, Lambrechts D, Li N, Lindblom A, Long J, Lophatananon A, Lubinski J, Mannermaa A, Manoukian S, Margolin S, Matsuo K, Meindl A, Mitchell G, Muir K, Nevelsteen I, van den Ouweland A, Peterlongo P, Phuah SY, Pylkäs K, Rowley SM, Sangrajrang S, Schmutzler RK, Shen CY, Shu XO, Southey MC, Surowy H, Swerdlow A, Teo SH, Tollenaar RA, Tomlinson I, Torres D, Truong T, Vachon C, Verhoef S, Wong-Brown M, Zheng W, Zheng Y, Nevanlinna H, Scott RJ, Andrulis IL, Wu AH, Hopper JL, Couch FJ, Winqvist R, Burwinkel B, Sawyer EJ, Schmidt MK, Rudolph A, Dörk T, Brauch H, Hamann U, Neuhausen SL, Milne RL, Fletcher O, Pharoah PD, Campbell IG, Dunning AM, Le Calvez-Kelm F, Goldgar DE, Tavtigian SV, Chenevix-Trench G. Australian Ovarian Cancer Study Group kConFab Investigators Lifepool Investigators NBCS Investigators. No evidence that protein truncating variants in BRIP1 are associated with breast cancer risk: implications for gene panel testing. *J Med Genet* 2016;53:298–309.
8 Benusiglio PR. CDH1 germline mutations: different syndromes, same management? *Genet Med* 2017;19:965–6.
9 van der Post RS, Vogelaar IP, Carneiro F, Guilford P, Huntsman D, Hoogerbrugge N, Caldas C, Schreiber KE, Hardwick RH, Ausems MG, Bardram L, Benusiglio PR, Bisseling TM, Blair V, Bleiker E, Boussioutas A, Cats A, Coit D, DeGregorio L, Figueiredo J, Ford JM, Heijkoop E, Hermens R, Humar B, Kaurah P, Keller G, Lai J, Ligtenberg MJ, O'Donovan M, Oliveira C, Pinheiro H, Ragunath K, Rasenberg E, Richardson S, Roviello F, Schackert H, Seruca R, Taylor A, Ter Huurne A, Tischkowitz M, Joe ST, van Dijck B, van Grieken NC, van Hillegersberg R, van Sandick JW, Vehof R, van Krieken JH, Fitzgerald RC. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. *J Med Genet* 2015;52:361–74.
10 Michailidou K, Beesley J, Lindstrom S, Canisius S, Dennis J, Lush MJ, Maranian MJ, Bolla MK, Wang Q, Shah M, Perkins BJ, Czene K, Eriksson M, Darabi H, Brand JS, Bojesen SE, Nordestgaard BG, Flyger H, Nielsen SF, Rahman N, Turnbull C, Fletcher O, Peto J, Gibson L, dos-Santos-Silva I, Chang-Claude J, Flesch-Janys D, Rudolph A, Eilber U, Behrens S, Nevanlinna H, Muranen TA, Aittomäki K, Blomqvist C, Khan S, Aaltonen K, Ahsan H, Kibriya MG, Whittemore AS, John EM, Malone KE, Gammon MD, Santella RM, Ursin G, Makalic E, Schmidt DF, Casey G, Hunter DJ, Gapstur SM, Gaudet MM, Diver WR, Haiman CA, Schumacher F, Henderson BE, Le Marchand L, Berg CD, Chanock SJ, Figueroa J, Hoover RN, Lambrechts D, Neven P, Wildiers H, van Limbergen E, Schmidt MK, Broeks A, Verhoef S, Cornelissen S, Couch FJ, Olson JE, Hallberg E, Vachon C, Waisfisz Q, Meijers-Heijboer H, Adank MA, van der Luijt RB, Li J, Liu J, Humphreys K, Kang D, Choi JY, Park SK, Yoo KY, Matsuo K, Ito H, Iwata H, Tajima K, Guénel P, Truong T, Mulot C, Sanchez M, Burwinkel B, Marme F, Surowy H, Sohn C, Wu AH, Tseng CC, Van Den Berg D, Stram DO, González-Neira A, Benitez J, Zamora MP, Perez JI, Shu XO, Lu W, Gao YT, Cai H, Cox A, Cross SS, Reed MW, Andrulis IL, Knight JA, Glendon G, Mulligan AM, Sawyer EJ, Tomlinson I, Kerin MJ, Miller N, Lindblom A, Margolin S, Teo SH, Yip CH, Taib NA, Tan GH, Hooning MJ, Hollestelle A, Martens JW, Collée JM, Blot W, Signorello LB, Cai Q, Hopper JL, Southey MC, Tsimiklis H, Apicella C, Shen CY, Hsiung CN, Wu PE, Hou MF, Kristensen VN, Nord S, Alnaes GI, Giles GG, Milne RL, McLean C, Canzian F, Trichopoulos D, Peeters P, Lund E, Sund M, Khaw KT, Gunter MJ, Palli D, Mortensen LM, Dossus L, Huerta JM, Meindl A, Schmutzler RK, Sutter C, Yang R, Muir K, Lophatananon A, Stewart-Brown S, Siriwanarangsan P, Hartman M, Miao H, Chia KS, Chan CW, Fasching PA, Hein A, Beckmann MW, Haeberle L, Brenner H, Dieffenbach AK, Arndt V, Stegmaier C, Ashworth A, Orr N, Schoemaker MJ, Swerdlow AJ, Brinton L, Garcia-Closas M, Zheng W, Halverson SL, Shrubsole M, Long J, Goldberg MS, Labrèche F, Dumont M, Winqvist R, Pylkäs K, Jukkola-Vuorinen A, Grip M, Brauch H, Hamann U, Brüning T, Radice P, Peterlongo P, Manoukian S, Bernard L, Bogdanova NV, Dörk T, Mannermaa A, Kataja V, Kosma VM, Hartikainen JM, Devilee P, Tollenaar RA, Seynaeve C, Van Asperen CJ, Jakubowska A, Lubinski J, Jaworska K, Huzarski T, Sangrajrang S, Gaborieau V, Brennan P, McKay J, Slager S, Toland AE, Ambrosone CB, Yannoukakos D, Kabisch M, Torres D, Neuhausen SL, Anton-Culver H, Luccarini C, Baynes C, Ahmed S, Healey CS, Tessier DC, Vincent D, Bacot F, Pita G, Alonso MR, Álvarez N, Herrero D, Simard J, Pharoah PP, Kraft P, Dunning AM, Chenevix-Trench G, Hall P, Easton DF. BOCS kConFab Investigators AOCS Group NBCS GENICA Network. Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. *Nat Genet* 2015;47:373–80.
11 Mavaddat N, Pharoah PD, Michailidou K, Tyrer J, Brook MN, Bolla MK, Wang Q, Dennis J, Dunning AM, Shah M, Luben R, Brown J, Bojesen SE, Nordestgaard BG, Nielsen SF, Flyger H, Czene K, Darabi H, Eriksson M, Peto J, Dos-Santos-Silva I, Dudbridge F, Johnson N, Schmidt MK, Broeks A, Verhoef S, Rutgers EJ, Swerdlow A, Ashworth A, Orr N, Schoemaker MJ, Figueroa J, Chanock SJ, Brinton L, Lissowska J, Couch FJ, Olson JE, Vachon C, Pankratz VS, Lambrechts D, Wildiers H, Van Ongeval C, van Limbergen E, Kristensen V, Grenaker Alnæs G, Nord S, Borresen-Dale AL, Nevanlinna H, Muranen TA, Aittomäki K, Blomqvist C, Chang-Claude J, Rudolph A, Seibold P, Flesch-Janys D, Fasching PA, Haeberle L, Ekici AB, Beckmann MW, Burwinkel B, Marme F, Schneeweiss A, Sohn C, Trentham-Dietz A, Newcomb P, Titus L, Egan KM, Hunter DJ, Lindstrom S, Tamimi RM, Kraft P, Rahman N, Turnbull C, Renwick A, Seal S, Li J, Liu J, Humphreys K, Benitez J, Pilar Zamora M, Arias Perez JI, Menéndez P, Jakubowska A, Lubinski J, Jaworska-Bieniek K, Durda K, Bogdanova NV, Antonenkova NN, Dörk T, Anton-Culver H, Neuhausen SL, Ziogas A, Bernstein L, Devilee P, Tollenaar RA, Seynaeve C, van Asperen CJ, Cox A, Cross SS, Reed MW, Khusnutdinova E, Bermisheva M, Prokofyeva D, Takhirova Z, Meindl A, Schmutzler RK, Sutter C, Yang R, Schürmann P, Bremer M, Christiansen H, Park-Simon TW, Hillemanns P, Guénel P, Truong T, Menegaux F, Sanchez M, Radice P, Peterlongo P, Manoukian S, Pensotti V, Hopper JL, Tsimiklis H, Apicella C, Southey MC, Brauch H, Brüning T, Ko YD, Sigurdson AJ, Doody MM, Hamann U, Torres D, Ulmer HU, Försti A, Sawyer EJ, Tomlinson I, Kerin MJ, Miller N, Andrulis IL, Knight JA, Glendon G, Marie Mulligan A, Chenevix-Trench G, Balleine R, Giles GG, Milne RL, McLean C, Lindblom A, Margolin S, Haiman CA, Henderson BE, Schumacher F, Le Marchand L, Eilber U, Wang-Gohrke S, Hooning MJ, Hollestelle A, van den Ouweland AM, Koppert LB, Carpenter J, Clarke C, Scott R, Mannermaa A, Kataja V, Kosma VM, Hartikainen JM, Brenner H, Arndt V, Stegmaier C, Karina Dieffenbach A, Winqvist R, Pylkäs K, Jukkola-Vuorinen A, Grip M, Offit K, Vijai J, Robson M, Rau-Murthy R, Dwek M, Swann R, Annie Perkins K, Goldberg MS, Labrèche F, Dumont M, Eccles DM, Tapper WJ, Rafiq S, John EM, Whittemore AS, Slager S, Yannoukakos D, Toland AE, Yao S, Zheng W, Halverson SL, González-Neira A, Pita G, Rosario Alonso M, Álvarez N, Herrero D, Tessier DC, Vincent D, Bacot F, Luccarini C, Baynes C, Ahmed S, Maranian M, Healey CS, Simard J, Hall P, Easton DF, Garcia-Closas M. Prediction of breast cancer risk based on profiling with common genetic variants. *J Natl Cancer Inst* 2015;107.
12 Ramus SJ, Song H, Dicks E, Tyrer JP, Rosenthal AN, Intermaggio MP, Fraser L, Gentry-Maharaj A, Hayward J, Philpott S, Anderson C, Edlund CK, Conti D, Harrington P, Barrowdale D, Bowtell DD, Alsop K, Mitchell G, Cicek MS, Cunningham JM, Fridley BL, Alsop J, Jimenez-Linan M, Poblete S, Lele S, Sucheston-Campbell L, Moysich KB, Sieh W, McGuire V, Lester J, Bogdanova N, Dürst M, Hillemanns P, Odunsi K, Whittemore AS, Karlan BY, Dörk T, Goode EL, Menon U, Jacobs IJ, Antoniou AC, Pharoah PD, Gayther SA. AOCS Study Group Ovarian Cancer Association Consortium. Germline Mutations in the BRIP1, BARD1, PALB2, and NBN genes in women with ovarian cancer. *J Natl Cancer Inst* 2015;107.
13 Ligtenberg MJ, Kuiper RP, Geurts van Kessel A, Hoogerbrugge N. EPCAM deletion carriers constitute a unique subgroup of Lynch syndrome patients. *Fam Cancer* 2013;12:169–74.
14 Ruijs MWG, Verhoef S, Rookus MA, Pruntel R, van der Hout AH, Hogervorst FBL, Kluijt I, Sijmons RH, Aalfs CM, Wagner A, Ausems MGEM, Hoogerbrugge N, van Asperen CJ, Gomez Garcia EB, Meijers-Heijboer H, ten Kate LP, Menko FH, van 't Veer LJ. TP53 germline mutation testing in 180 families suspected of Li-Fraumeni syndrome: mutation detection rate and relative frequency of cancers in different familial phenotypes. *J Med Genet* 2010;47:421–8.
15 Møller P, Seppälä TT, Bernstein I, Holinski-Feder E, Sala P, Gareth Evans D, Lindblom A, Macrae F, Blanco I, Sijmons RH, Jeffries J, Vasen HFA, Burn J, Nakken S, Hovig E, Rødland EA, Tharmaratnam K, de Vos Tot Nederveen Cappel WH, Hill J, Wijnen JT, Jenkins MA, Green K, Lalloo F, Sunde L, Mints M, Bertario L, Pineda M, Navarro M, Morak M, Renkonen-Sinisalo L, Valentin MD, Frayling IM, Plazzer JP, Pylvanainen K, Genuardi M, Mecklin JP, Moeslein G, Sampson JR, Capella G. Mallorca Group. Cancer risk and survival in*path_MMR*carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. *Gut* 2017 [Epub ahead of print 28 Jul 2017].
16 Foulkes WD, Gore M, McCluggage WG. Rare non-epithelial ovarian neoplasms: Pathology, genetics and treatment. *Gynecol Oncol* 2016;142:190–8.
17 Broderick P, Dobbins SE, Chubb D, Kinnersley B, Dunlop MG, Tomlinson I, Houlston RS. Validation of recently proposed colorectal cancer susceptibility gene variants in an analysis of families and patients—a systematic review. *Gastroenterology* 2017;152:75–7.
18 The Ataxia-Telangiectasia Society. Ataxia-telangiectasia in children: Guidance on diagnosis and clinical care 2014. http://www.atsociety.org.uk/data/files/William/A-T_Clinical_Guidance_Document_Final.pdf
19 Public Health England. Protocols for the surveillance of women at higher risk of developing breast cancer 2013. https://www.gov.uk/government/publications/breast-screening-higher-risk-women-surveillance-protocols2017
20 NICE. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer 2017. https://www.nice.org.uk/guidance/cg164/2017
21 Tung N, Domchek SM, Stadler Z, Nathanson KL, Couch F, Garber JE, Offit K, Robson ME. Counselling framework for moderate-penetrance cancer-susceptibility mutations. *Nat Rev Clin Oncol* 2016;13:581–8.
22 UK Cancer Genetics Group. Guidelines for management of tumour risk in PTEN hamartoma syndrome. 2017 http://www.ukcgg.org/media/1099545/pten_management_-_cgg_4may2017.pdf.

23 Beggs AD, Latchford AR, Vasen HFA, Moslein G, Alonso A, Aretz S, Bertario L, Blanco I, Bulow S, Burn J, Capella G, Colas C, Friedl W, Moller P, Hes FJ, Jarvinen H, Mecklin J-P, Nagengast FM, Parc Y, Phillips RKS, Hyer W, Ponz de Leon M, Renkonen-Sinisalo L, Sampson JR, Stormorken A, Tejpar S, Thomas HJW, Wijnen JT, Clark SK, Hodgson SV. Peutz-Jeghers syndrome: a systematic review and recommendations for management. *Gut* 2010;59:975–86.

24 Lee AJ, Cunningham AP, Tischkowitz M, Simard J, Pharoah PD, Easton DF, Antoniou AC. Incorporating truncating variants in PALB2, CHEK2 and ATM into the BOADICEA breast cancer risk model. *Genetics in Medicine* 2016;18:1190–8.

25 Vasen HF, Blanco I, Aktan-Collan K, Gopie JP, Alonso A, Aretz S, Bernstein I, Bertario L, Burn J, Capella G, Colas C, Engel C, Frayling IM, Genuardi M, Heinimann K, Hes FJ, Hodgson SV, Karagiannis JA, Lalloo F, Lindblom A, Mecklin JP, Møller P, Myrhoj T, Nagengast FM, Parc Y, Ponz de Leon M, Renkonen-Sinisalo L, Sampson JR, Stormorken A, Sijmons RH, Tejpar S, Thomas HJ, Rahner N, Wijnen JT, Järvinen HJ, Möslein G. Mallorca group. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. *Gut* 2013;62:812–23.

26 Daly MB, Pilarski R, Berry M, Buys SS, Farmer M, Friedman S, Garber JE, Kauff ND, Khan S, Klein C, Kohlmann W, Kurian A, Litton JK, Madlensky L, Merajver SD, Offit K, Pal T, Reiser G, Shannon KM, Swisher E, Vinayak S, Voian NC, Weitzel JN, Wick MJ, Wiesner GL, Dwyer M, Darlow S. NCCN guidelines insights: genetic/familial high-risk assessment: breast and ovarian, version 2.2017. *J Natl Compr Canc Netw* 2017;15:9–20.

27 Vasen HFA, Moslein G, Alonso A, Aretz S, Bernstein I, Bertario L, Blanco I, Bulow S, Burn J, Capella G, Colas C, Engel C, Frayling I, Friedl W, Hes FJ, Hodgson S, Jarvinen H, Mecklin J-P, Moller P, Myrhoi T, Nagengast FM, Parc Y, Phillips R, Clark SK, de Leon MP, Renkonen-Sinisalo L, Sampson JR, Stormorken A, Tejpar S, Thomas HJW, Wijnen J. Guidelines for the clinical management of familial adenomatous polyposis (FAP). *Gut* 2008;57:704–13.

28 Cairns SR, Scholefield JH, Steele RJ, Dunlop MG, Thomas HJ, Evans GD, Eaden JA, Rutter MD, Atkin WP, Saunders BP, Lucassen A, Jenkins P, Fairclough PD, Woodhouse CR. British Society of Gastroenterology Association of Coloproctology for Great Britain and Ireland. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). *Gut* 2010;59:666–89.

29 Møller P, Seppälä T, Bernstein I, Holinski-Feder E, Sala P, Evans DG, Lindblom A, Macrae F, Blanco I, Sijmons R, Jeffries J, Vasen H, Burn J, Nakken S, Hovig E, Rødland EA, Tharmaratnam K, de Vos Tot Nederveen Cappel WH, Hill J, Wijnen J, Green K, Lalloo F, Sunde L, Mints M, Bertario L, Pineda M, Navarro M, Morak M, Renkonen-Sinisalo L, Frayling IM, Plazzer JP, Pylvanainen K, Sampson JR, Capella G, Mecklin JP, Möslein G. Mallorca Group (http://mallorca-group.eu). Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. *Gut* 2017;66:464–72.