OncoGeneDx: Breast/Gyn Cancer Panel

Panel Gene List: *ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM*, FANCC, FANCM, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, POLD1, PTEN, RAD51C, RAD51D, RECQL,TP53*

*Testing includes sequencing and deletion/duplication analysis for all genes except *EPCAM* (del/dup only).

Clinical Features:

In the general population, approximately 1 in 8 women (12%) will develop breast cancer in their lifetime, 1 in 75 women (1.4%) will be diagnosed with ovarian cancer in their lifetime, and 1 in 36 women (2.8%) will develop endometrial cancer, also known as uterine cancer.[1]
Most cases of breast, ovarian, and endometrial cancer develop sporadically with no family history of the cancer. However, 5-10% of breast and endometrial cancer cases and 15-20% of ovarian cancer cases are due to a hereditary predisposition. The features of a personal and/or family history of cancer that are suggestive of a hereditary cancer predisposition include: young age at diagnosis, multiple primary cancers in a single individual, diagnosis of a cancer type that is not common in general population (such as ovarian cancer, male breast cancer, or pancreatic cancer), and several relatives affected with related cancers spanning multiple generations.

Approximately 20-25% of familial breast cancer risk is thought to be attributed to pathogenic variants in the *BRCA1* and *BRCA2* genes.[2–4] The additional 21 genes on this panel may also account for a substantial proportion of hereditary breast, ovarian, and endometrial cancer cases. Many of these genes are involved in the Fanconi anemia pathway and/or play a role in DNA damage repair similar to the *BRCA1* and *BRCA2* genes. Newer genes, such as *BARD1*, *FANCC*, and *RECQL*, have been identified in families with breast and/or ovarian cancer and have been included in the panel to make it as comprehensive as possible. The evidence available to date may be derived from a small number of patients with wide confidence intervals or is based upon an ethnic cohort with one specific variant. Accurate risk assessment may be complicated by the low penetrance of pathogenic variants in these genes and/or ascertainment bias. Since the cancer risks are not yet well defined, no consensus guidelines for medical management are available for these genes.

Inheritance Pattern:

Most genes on this panel are associated with an autosomal dominant cancer risk with the exception of *MUTYH*, which is associated with an autosomal recessive cancer risk. Some of the genes on this panel are also associated with extremely rare conditions when inherited in an autosomal recessive fashion. The specifics of this inheritance are outlined in the table below.

Test Methods:
Genomic DNA is extracted from the submitted specimen. For skin punch biopsies, fibroblasts are cultured and used for DNA extraction. This DNA is enriched for the complete coding regions and splice site junctions of the genes on this panel using a proprietary targeted capture system developed by GeneDx for next generation sequencing with CNV calling (NGS-CNV). For *PTEN* nucleotides c.-700 through c.-1300 in the promoter region are also captured. The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Concurrent *MSH2* Exons 1-7 Inversion analysis from NGS data is also performed. For *EPCAM*, deletion/duplication analysis, but not sequencing, is performed. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

Test Sensitivity:
The clinical sensitivity of sequencing and deletion/duplication analysis of the 24 genes included in the OncoGeneDx Breast/Gyn Cancer Panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with features suggestive of a hereditary predisposition to cancer as outlined above. DNA sequencing will detect nucleotide substitutions and small insertions and deletions, while NGS-CNV analysis, array CGH, or MLPA will detect exon-level deletions and duplications. These methods are expected to be greater than 99% sensitive in detecting pathogenic variants identifiable by sequencing or CNV technology.

Genetic testing using the methods applied at GeneDx is expected to be highly accurate. Normal findings do not rule out the diagnosis of a genetic disorder since some genetic abnormalities may be undetectable by this test. The methods used cannot reliably detect deletions of 20bp to 250bp in size, or insertions of 10bp to 250 bp in size. Sequencing cannot detect low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect mosaicism and cannot identify balanced chromosome aberrations. Rarely, incidental findings of large chromosomal rearrangements outside the gene of interest may be identified. Regions of certain genes have inherent sequence properties (for example: repeat, homology, or pseudogene regions, high GC content, rare polymorphisms) that yield suboptimal data, potentially impairing accuracy of the results. False negatives may also occur in the setting of bone marrow transplantation, recent blood transfusion, or suboptimal DNA quality. In

individuals with active or chronic hematologic neoplasms or conditions, there is a possibility that testing may detect an acquired somatic variant, resulting in a false positive result. As the ability to detect genetic variants and naming conventions can differ among laboratories, rare false negative results may occur when no positive control is provided for testing of a specific variant identified at another laboratory. The chance of a false positive or false negative result due to laboratory errors incurred during any phase of testing cannot be completely excluded. Interpretations are made with the assumption that any clinical information provided, including family relationships, are accurate. Consultation with a genetics professional is recommended for interpretation of results.

Gene	Protein	Inheritance	Disease Associations
ATM [5–10]	SERINE-PROTEIN KINASE ATM	AD	Breast, colon & pancreatic cancers
		AR	Ataxia telangiectasia
BARD1 [11–13]	BRCA1-ASSOCIATED RING DOMAIN PROTEIN 1	AD	Breast & ovarian cancer
BRCA1 [14–24]	BREAST CANCER TYPE 1 SUSCEPTIBILITY PROTEIN	AD	Hereditary Breast and Ovarian Cancer (HBOC) syndrome: breast, ovarian, pancreatic, prostate & endometrial serous cancer
BRCA2 [14–21,23,24]	BREAST CANCER TYPE 2 SUSCEPTIBILITY PROTEIN	AD	Hereditary Breast and Ovarian Cancer (HBOC) syndrome: breast, ovarian, pancreatic, prostate, melanoma & endometrial serous cancer
		AR	Fanconi anemia
BRIP1 [5,25–27]	FANCONI ANEMIA GROUP J PROTEIN	AD	Breast & ovarian cancer
		AR	Fanconi anemia
CDH1 [28–34]	CADHERIN 1	AD	Hereditary Diffuse Gastric Cancer (HDGC) syndrome: gastric (diffuse), breast & colon (signet ring) cancer
CHEK2 [5,6,22,35–41]	SERINE/THREONINE-PROTEIN KINASE CHK2	AD	Breast, colon, prostate, gastric & thyroid cancer
EPCAM [42–47]	EPITHELIAL CELL ADHESION MOLECULE	AD	Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate & brain cancer, sebaceous neoplasms

Gene	Protein	Inheritance	Disease Associations
		AR	Constitutional mismatch repair deficiency syndrome
FANCC[48,49]	FANCONI ANEMIA GROUP C PROTEIN	AD	Breast cancer
		AR	Fanconi anemia
FANCM[50–52]	FANCONI ANEMIA GROUP M PROTEIN	AD	Breast & ovarian cancer
		AR	Fanconi anemia-like cancer susceptibility
MLH1[42,44–47,53,54]	DNA MISMATCH REPAIR PROTEIN MLH1	AD	Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate & brain cancer, sebaceous neoplasms
		AR	Constitutional mismatch repair deficiency syndrome
MSH2[42–47,53,54]	DNA MISMATCH REPAIR PROTEIN MSH2	AD	Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate & brain cancer, sebaceous neoplasms
		AR	Constitutional mismatch repair deficiency syndrome
MSH6[42,44–47,53,55]	DNA MISMATCH REPAIR PROTEIN MSH6	AD	Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate & brain cancer, sebaceous neoplasms
		AR	Constitutional mismatch repair deficiency syndrome
MUTYH[56–68]	ADENINE DNA GLYCOSYLASE	AR	*MUTYH*-associated polyposis (MAP): colorectal, small bowel & endometrial serous cancer, gastrointestinal polyps
NBN[69–75]	NIBRIN	AD	Breast & prostate cancer, non-Hodgkin lymphoma
		AR	Nijmegen breakage syndrome
NF1[76–78]	NEUROFIBROMIN	AD	Neurofibromatosis type 1

Gene	Protein	Inheritance	Disease Associations
			(NF1) syndrome: breast cancer, GIST, optic nerve gliomas, pheochromocytoma, MPNST, neurofibromas, brain tumors
PALB2[5,79–84]	PARTNER AND LOCALIZER OF BRCA2	AD	Breast, pancreatic & ovarian cancer
		AR	Fanconi anemia
PMS2[42,44–47,85,86]	MISMATCH REPAIR ENDONUCLEASE PMS2	AD	Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate & brain cancer, sebaceous neoplasms
		AR	Constitutional mismatch repair deficiency syndrome
POLD1[87,88]	DNA POLYPMERASE DELTA CATALYTIC SUBUNIT	AD	Colon & endometrial cancer, colon polyps
PTEN[56,89–92]	PHOSPHATIDYLINOSITOL 3,4,5-TRISPHOSPHATE 3-PHOSPHATASE AND DUAL-SPECIFICITY PROTEIN PHOSPHATASE PTEN	AD	*PTEN* hamartoma tumor syndrome (PHTS): breast, thyroid, endometrial, colon, melanoma & renal cancer, gastrointestinal polyps, Lhermitte-Duclos disease
RAD51C[93–96]	DNA REPAIR PROTEIN RAD51 HOMOLOG 3	AD	Breast & ovarian cancer
		AR	Fanconi anemia
RAD51D[93,94,97,98]	DNA REPAIR PROTEIN RAD51 HOMOLOG 4	AD	Breast & ovarian cancer
RECQL[99–102]	RECQ PROTEIN-LIKE	AD	Breast cancer
TP53[22,103–107]	CELLULAR TUMOR ANTIGEN P53	AD	Li-Fraumeni syndrome (LFS): breast cancer, sarcoma, brain cancer, hematologic malignancies, adrenocortical carcinoma, among others**

Because of evolving and expanding phenotypes, this list of cancer/tumor types is not exhaustive. Gene-specific risk for some of the cancers and other features listed are not well-defined.

** High overall risk of cancer: 75% lifetime risk for males to develop cancer, nearly 100% risk for females.

Abbreviations:
AD – Autosomal Dominant
AR – Autosomal Recessive
CGH – Comparative genomic hybridization
MLPA – Multiplex ligation-dependent probe amplification
MPNST - Malignant peripheral nerve sheath tumors
GIST – Gastrointestinal stromal tumor

References:

1. Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. SEER Cancer Statistics Review, 1975-2012: Lifetime Risk Tables (URL: http://surveillance.cancer.gov/devcan) [October 2016 accessed].
2. Easton, D. F. How many more breast cancer predisposition genes are there? Breast Cancer Res. BCR **1**, 14–17 (1999).
3. Pharoah, P. D. P. et al. Polygenic susceptibility to breast cancer and implications for prevention. Nat. Genet. **31**, 33–36 (2002).
4. van der Groep, P., van der Wall, E. & van Diest, P. J. Pathology of hereditary breast cancer. Cell. Oncol. Dordr. **34**, 71–88 (2011).
5. Byrnes, G. B., Southey, M. C. & Hopper, J. L. Are the so-called low penetrance breast cancer genes, ATM, BRIP1, PALB2 and CHEK2, high risk for women with strong family histories? Breast Cancer Res. BCR **10**, 208 (2008).
6. Einarsdóttir, K. et al. Effect of ATM, CHEK2 and ERBB2 TAGSNPs and haplotypes on endometrial cancer risk. Hum. Mol. Genet. **16**, 154–164 (2007).
7. Renwick, A. et al. ATM mutations that cause ataxia-telangiectasia are breast cancer susceptibility alleles. Nat. Genet. **38**, 873–875 (2006).
8. Roberts, N. J. et al. ATM mutations in patients with hereditary pancreatic cancer. Cancer Discov. **2**, 41–46 (2012).
9. Tavtigian, S. V. et al. Rare, evolutionarily unlikely missense substitutions in ATM confer increased risk of breast cancer. Am. J. Hum. Genet. **85**, 427–446 (2009).
10. Thompson, D. et al. Cancer risks and mortality in heterozygous ATM mutation carriers. J. Natl. Cancer Inst. **97**, 813–822 (2005).
11. De Brakeleer, S. et al. Cancer predisposing missense and protein truncating BARD1 mutations in non-BRCA1 or BRCA2 breast cancer families. Hum. Mutat. **31**, E1175-1185 (2010).
12. De Brakeleer, S. et al. Frequent incidence of BARD1-truncating mutations in germline DNA from triple-negative breast cancer patients. Clin. Genet. **89**, 336–340 (2016).
13. Couch, F. J. et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. **33**, 304–311 (2015).
14. Ford, D. et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am. J. Hum. Genet. **62**, 676–689 (1998).
15. Antoniou, A. et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am. J. Hum. Genet. **72**, 1117–1130 (2003).
16. Biron-Shental, T., Drucker, L., Altaras, M., Bernheim, J. & Fishman, A. High incidence of BRCA1-2 germline mutations, previous breast cancer and familial cancer history in Jewish patients with uterine serous papillary carcinoma. Eur. J. Surg. Oncol. J. Eur. Soc. Surg. Oncol. Br. Assoc. Surg. Oncol. **32**, 1097–1100 (2006).
17. Chen, S. & Parmigiani, G. Meta-analysis of BRCA1 and BRCA2 penetrance. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. **25**, 1329–1333 (2007).
18. Graeser, M. K. et al. Contralateral breast cancer risk in BRCA1 and BRCA2 mutation carriers. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. **27**, 5887–5892 (2009).
19. King, M.-C., Marks, J. H., Mandell, J. B. & New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science **302**, 643–646 (2003).
20. Liede, A., Karlan, B. Y. & Narod, S. A. Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. **22**, 735–742 (2004).
21. Levine, D. A. et al. Fallopian tube and primary peritoneal carcinomas associated with BRCA mutations. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. **21**, 4222–4227 (2003).
22. Pennington, K. P. et al. BRCA1, TP53, and CHEK2 germline mutations in uterine serous carcinoma. Cancer **119**, 332–338 (2013).
23. Risch, H. A. et al. Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. J. Natl. Cancer Inst. **98**, 1694–1706 (2006).
24. Claus, E. B., Schildkraut, J. M., Thompson, W. D. & Risch, N. J. The genetic attributable risk of breast and ovarian cancer. Cancer **77**, 2318–2324 (1996).
25. Ramus, S. J. et al. Germline Mutations in the BRIP1, BARD1, PALB2, and NBN Genes in Women With Ovarian Cancer. J. Natl. Cancer Inst. **107**, (2015).
26. Pritchard, C. C. et al. Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. N. Engl. J. Med. **375**, 443–453 (2016).
27. Ghazwani, Y. et al. Clinical characteristics and genetic subtypes of Fanconi anemia in Saudi patients. Cancer Genet. **209**, 171–176 (2016).
28. Fitzgerald, R. C. et al. Hereditary diffuse gastric cancer: updated consensus guidelines for clinical management and directions for future research. J. Med. Genet. **47**, 436–444 (2010).
29. Kaurah, P. et al. Founder and recurrent CDH1 mutations in families with hereditary diffuse gastric cancer. JAMA **297**, 2360–2372 (2007).
30. Petridis, C. et al. Germline CDH1 mutations in bilateral lobular carcinoma in situ. Br. J. Cancer **110**, 1053–1057 (2014).

31. Pharoah, P. D., Guilford, P., Caldas, C. & International Gastric Cancer Linkage Consortium. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. Gastroenterology **121**, 1348–1353 (2001).
32. Schrader, K. A. et al. Germline mutations in CDH1 are infrequent in women with early-onset or familial lobular breast cancers. J. Med. Genet. **48**, 64–68 (2011).
33. Brooks-Wilson, A. R. et al. Germline E-cadherin mutations in hereditary diffuse gastric cancer: assessment of 42 new families and review of genetic screening criteria. J. Med. Genet. **41**, 508–517 (2004).
34. Guilford, P. et al. E-cadherin germline mutations in familial gastric cancer. Nature **392**, 402–405 (1998).
35. Cybulski, C. et al. CHEK2 is a multiorgan cancer susceptibility gene. Am. J. Hum. Genet. **75**, 1131–1135 (2004).
36. Dong, X. et al. Mutations in CHEK2 associated with prostate cancer risk. Am. J. Hum. Genet. **72**, 270–280 (2003).
37. Han, F., Guo, C. & Liu, L. The effect of CHEK2 variant I157T on cancer susceptibility: evidence from a meta-analysis. DNA Cell Biol. **32**, 329–335 (2013).
38. Kilpivaara, O., Alhopuro, P., Vahteristo, P., Aaltonen, L. A. & Nevanlinna, H. CHEK2 I157T associates with familial and sporadic colorectal cancer. J. Med. Genet. **43**, e34 (2006).
39. Liu, C., Wang, Q.-S. & Wang, Y.-J. The CHEK2 I157T variant and colorectal cancer susceptibility: a systematic review and meta-analysis. Asian Pac. J. Cancer Prev. APJCP **13**, 2051–2055 (2012).
40. Seppälä, E. H. et al. CHEK2 variants associate with hereditary prostate cancer. Br. J. Cancer **89**, 1966–1970 (2003).
41. Suchy, J. et al. CHEK2 mutations and HNPCC-related colorectal cancer. Int. J. Cancer **126**, 3005–3009 (2010).
42. Weissman, S. M. et al. Genetic counseling considerations in the evaluation of families for Lynch syndrome--a review. J. Genet. Couns. **20**, 5–19 (2011).
43. Li-Chang, H. H. et al. Colorectal cancer in a 9-year-old due to combined EPCAM and MSH2 germline mutations: case report of a unique genotype and immunophenotype. J. Clin. Pathol. **66**, 631–633 (2013).
44. Durno, C. A., Holter, S., Sherman, P. M. & Gallinger, S. The gastrointestinal phenotype of germline biallelic mismatch repair gene mutations. Am. J. Gastroenterol. **105**, 2449–2456 (2010).
45. Vasen, H. F. et al. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. Gastroenterology **110**, 1020–1027 (1996).
46. Wimmer, K. & Kratz, C. P. Constitutional mismatch repair-deficiency syndrome. Haematologica **95**, 699–701 (2010).
47. Win, A. K. et al. Colorectal and other cancer risks for carriers and noncarriers from families with a DNA mismatch repair gene mutation: a prospective cohort study. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. **30**, 958–964 (2012).
48. Berwick, M. et al. Genetic heterogeneity among Fanconi anemia heterozygotes and risk of cancer. Cancer Res. **67**, 9591–9596 (2007).
49. Thompson, E. R. et al. Exome sequencing identifies rare deleterious mutations in DNA repair genes FANCC and BLM as potential breast cancer susceptibility alleles. PLoS Genet. **8**, e1002894 (2012).
50. Bogliolo, M. et al. Biallelic truncating FANCM mutations cause early-onset cancer but not Fanconi anemia. Genet. Med. Off. J. Am. Coll. Med. Genet. **20**, 458–463 (2018).
51. Neidhardt, G. et al. Association Between Loss-of-Function Mutations Within the FANCM Gene and Early-Onset Familial Breast Cancer. JAMA Oncol. **3**, 1245–1248 (2017).
52. Dicks, E. et al. Germline whole exome sequencing and large-scale replication identifies FANCM as a likely high grade serous ovarian cancer susceptibility gene. Oncotarget **8**, 50930–50940 (2017).
53. Bonadona, V. et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA **305**, 2304–2310 (2011).
54. Quehenberger, F., Vasen, H. F. A. & van Houwelingen, H. C. Risk of colorectal and endometrial cancer for carriers of mutations of the hMLH1 and hMSH2 gene: correction for ascertainment. J. Med. Genet. **42**, 491–496 (2005).
55. Baglietto, L. et al. Risks of Lynch syndrome cancers for MSH6 mutation carriers. J. Natl. Cancer Inst. **102**, 193–201 (2010).
56. Jasperson, K. W. Genetic testing by cancer site: colon (polyposis syndromes). Cancer J. Sudbury Mass **18**, 328–333 (2012).
57. Sieber, O. M. et al. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH. N. Engl. J. Med. **348**, 791–799 (2003).
58. Balaguer, F. et al. Identification of MYH mutation carriers in colorectal cancer: a multicenter, case-control, population-based study. Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc. **5**, 379–387 (2007).
59. Barnetson, R. A. et al. Germline mutation prevalence in the base excision repair gene, MYH, in patients with endometrial cancer. Clin. Genet. **72**, 551–555 (2007).
60. Boparai, K. S. et al. Hyperplastic polyps and sessile serrated adenomas as a phenotypic expression of MYH-associated polyposis. Gastroenterology **135**, 2014–2018 (2008).
61. Croitoru, M. E. et al. Association between biallelic and monoallelic germline MYH gene mutations and colorectal cancer risk. J. Natl. Cancer Inst. **96**, 1631–1634 (2004).
62. Jenkins, M. A. et al. Risk of colorectal cancer in monoallelic and biallelic carriers of MYH mutations: a population-based case-family study. Cancer Epidemiol. Biomark. Prev. Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prev. Oncol. **15**, 312–314 (2006).

63. Lubbe, S. J., Di Bernardo, M. C., Chandler, I. P. & Houlston, R. S. Clinical implications of the colorectal cancer risk associated with MUTYH mutation. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. **27**, 3975–3980 (2009).
64. Out, A. A. et al. MUTYH gene variants and breast cancer in a Dutch case–control study. Breast Cancer Res. Treat. **134**, 219–227 (2012).
65. Santonocito, C. et al. Common genetic variants of MUTYH are not associated with cutaneous malignant melanoma: application of molecular screening by means of high-resolution melting technique in a pilot case-control study. Int. J. Biol. Markers **26**, 37–42 (2011).
66. Vogt, S. et al. Expanded extracolonic tumor spectrum in MUTYH-associated polyposis. Gastroenterology **137**, 1976-1985.e1–10 (2009).
67. Win, A. K. et al. Cancer risks for monoallelic MUTYH mutation carriers with a family history of colorectal cancer. Int. J. Cancer **129**, 2256–2262 (2011).
68. Cleary, S. P. et al. Germline MutY human homologue mutations and colorectal cancer: a multisite case-control study. Gastroenterology **136**, 1251–1260 (2009).
69. Slavin, T. P. et al. The contribution of pathogenic variants in breast cancer susceptibility genes to familial breast cancer risk. NPJ Breast Cancer **3**, 22 (2017).
70. Steffen, J. et al. Increased cancer risk of heterozygotes with NBS1 germline mutations in Poland. Int. J. Cancer **111**, 67–71 (2004).
71. Steffen, J. et al. Germline mutations 657del5 of the NBS1 gene contribute significantly to the incidence of breast cancer in Central Poland. Int. J. Cancer **119**, 472–475 (2006).
72. Gao, P., Ma, N., Li, M., Tian, Q.-B. & Liu, D.-W. Functional variants in NBS1 and cancer risk: evidence from a meta-analysis of 60 publications with 111 individual studies. Mutagenesis **28**, 683–697 (2013).
73. Buslov, K. G. et al. NBS1 657del5 mutation may contribute only to a limited fraction of breast cancer cases in Russia. Int. J. Cancer **114**, 585–589 (2005).
74. di Masi, A. & Antoccia, A. NBS1 Heterozygosity and Cancer Risk. Curr. Genomics **9**, 275–281 (2008).
75. He, Y.-Z. et al. NBS1 Glu185Gln polymorphism and cancer risk: update on current evidence. Tumour Biol. J. Int. Soc. Oncodevelopmental Biol. Med. **35**, 675–687 (2014).
76. Friedman, J. M. Neurofibromatosis 1. in GeneReviews® (eds. Adam, M. P. et al.) (University of Washington, Seattle, 1993).
77. Ferner, R. E. & Gutmann, D. H. Neurofibromatosis type 1 (NF1): diagnosis and management. Handb. Clin. Neurol. **115**, 939–955 (2013).
78. Ferner, R. E. et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J. Med. Genet. **44**, 81–88 (2007).
79. Rahman, N. et al. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. Nat. Genet. **39**, 165–167 (2007).
80. Erkko, H. et al. A recurrent mutation in PALB2 in Finnish cancer families. Nature **446**, 316–319 (2007).
81. Antoniou, A. C. et al. Breast-cancer risk in families with mutations in PALB2. N. Engl. J. Med. **371**, 497–506 (2014).
82. Casadei, S. et al. Contribution of inherited mutations in the BRCA2-interacting protein PALB2 to familial breast cancer. Cancer Res. **71**, 2222–2229 (2011).
83. Jones, S. et al. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. Science **324**, 217 (2009).
84. Slater, E. P. et al. PALB2 mutations in European familial pancreatic cancer families. Clin. Genet. **78**, 490–494 (2010).
85. Senter, L. et al. The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. Gastroenterology **135**, 419–428 (2008).
86. ten Broeke, S. W. et al. Lynch syndrome caused by germline PMS2 mutations: delineating the cancer risk. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. **33**, 319–325 (2015).
87. Palles, C. et al. Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. Nat. Genet. **45**, 136–144 (2013).
88. Bellido, F. et al. POLE and POLD1 mutations in 529 kindred with familial colorectal cancer and/or polyposis: review of reported cases and recommendations for genetic testing and surveillance. Genet. Med. Off. J. Am. Coll. Med. Genet. **18**, 325–332 (2016).
89. Bubien, V. et al. High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome. J. Med. Genet. **50**, 255–263 (2013).
90. Hobert, J. A. & Eng, C. PTEN hamartoma tumor syndrome: an overview. Genet. Med. Off. J. Am. Coll. Med. Genet. **11**, 687–694 (2009).
91. Nieuwenhuis, M. H. et al. Cancer risk and genotype-phenotype correlations in PTEN hamartoma tumor syndrome. Fam. Cancer **13**, 57–63 (2014).
92. Tan, M.-H. et al. Lifetime cancer risks in individuals with germline PTEN mutations. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. **18**, 400–407 (2012).
93. Norquist, B. M. et al. Inherited Mutations in Women With Ovarian Carcinoma. JAMA Oncol. **2**, 482–490 (2016).
94. Lilyquist, J. et al. Frequency of mutations in a large series of clinically ascertained ovarian cancer cases tested on multi-gene panels compared to reference controls. Gynecol. Oncol. **147**, 375–380 (2017).
95. Couch, F. J. et al. Associations Between Cancer Predisposition Testing Panel Genes and Breast Cancer. JAMA Oncol. **3**, 1190–1196 (2017).
96. Rashid, M. U., Muhammad, N., Faisal, S., Amin, A. & Hamann, U. Deleterious RAD51C germline mutations rarely predispose to breast and ovarian cancer in Pakistan. Breast Cancer Res. Treat. **145**, 775–784 (2014).

97. Loveday, C. et al. Germline mutations in RAD51D confer susceptibility to ovarian cancer. Nat. Genet. **43**, 879–882 (2011).
98. Song, H. et al. Contribution of Germline Mutations in the RAD51B, RAD51C, and RAD51D Genes to Ovarian Cancer in the Population. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. **33**, 2901–2907 (2015).
99. Sun, J. et al. Mutations in RECQL Gene Are Associated with Predisposition to Breast Cancer. PLoS Genet. **11**, e1005228 (2015).
100. Cybulski, C. et al. Germline RECQL mutations are associated with breast cancer susceptibility. Nat. Genet. **47**, 643–646 (2015).
101. Akbari, M. R. & Cybulski, C. RECQL: a DNA helicase in breast cancer. Oncotarget **6**, 26558–26559 (2015).
102. Kwong, A. et al. Germline RECQL mutations in high risk Chinese breast cancer patients. Breast Cancer Res. Treat. **157**, 211–215 (2016).
103. Chompret, A. et al. P53 germline mutations in childhood cancers and cancer risk for carrier individuals. Br. J. Cancer **82**, 1932–1937 (2000).
104. Gonzalez, K. D. et al. Beyond Li Fraumeni Syndrome: clinical characteristics of families with p53 germline mutations. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. **27**, 1250–1256 (2009).
105. Olivier, M. et al. Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype. Cancer Res. **63**, 6643–6650 (2003).
106. Ruijs, M. W. G. et al. 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. **47**, 421–428 (2010).
107. Hisada, M., Garber, J. E., Fung, C. Y., Fraumeni, J. F. & Li, F. P. Multiple primary cancers in families with Li-Fraumeni syndrome. J. Natl. Cancer Inst. **90**, 606–611 (1998).