OncoGeneDx: Custom Cancer Panel

Panel Gene List: *AIP, ALK, ANKRD26, APC, ATM, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDK4, CDKN1B, CDKN2A, CEBPA*, CHEK2, CTNNA1, DDX41, DICER1, EPCAM*, ETV6, FANCC, FANCM, FH, FLCN, GATA2, HOXB13, KIT, LZTR1, MAX, MEN1, MET, MITF, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, NF2, NTHL1, PALB2, PDGFRA, PHOX2B*, PMS2, POLD1, POLE, POT1, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RECQL, RET*, RUNX1, SAMD9, SAMD9L, SCG5/GREM1*, SDHA*, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, SRP72, STK11, SUFU, TERC, TERT, TMEM127, TP53, TSC1, TSC2, VHL, WT1*

*Testing includes sequencing and deletion/duplication analysis for all genes except *CEBPA* (seq only), *EPCAM* (del/dup only), *PHOX2B* (seq only), *RET* (seq only), *SCG5*/*GREM1* (del/dup only) and *SDHA* (seq only).

Clinical Features:

Cancer is a common disease affecting approximately 1 in 3 individuals in the U.S.[1] While the majority of cancers are sporadic in nature, some families have hereditary forms of cancer that are associated with increased cancer risks compared with the general population. Approximately 5-10% of cancer cases are thought to be due to a hereditary predisposition. Features that are suggestive of a hereditary cancer predisposition include: young ages at diagnosis, multiple primary cancers in a single individual, and several relatives affected with the same type of cancer or related cancers spanning multiple generations.

GeneDx offers a variety of hereditary cancer panels to facilitate testing of the genes related to certain types of cancer, such as the OncoGeneDx Breast/Gyn Cancer Panel or OncoGeneDx Colorectal Cancer Panel. However, GeneDx also offers the option of ordering single-gene testing and/or a customized cancer panel from a list of 83 cancer susceptibility genes. The option of ordering each gene individually or in any combination allows the provider the flexibility to choose the most appropriate testing approach for their patient when an available OncoGeneDx panel is not desired.

Many of the cancer genes offered at GeneDx are involved in the mismatch repair pathway, the Fanconi anemia pathway and/or DNA damage repair. Specifically, they are associated with common cancer syndromes such as Hereditary Breast and Ovarian Cancer Syndrome (*BRCA1*, *BRCA2*), Lynch Syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*) or are newly described cancer genes such as *AXIN2*, *NTHL1*, or *RECQL*. While the risks associated with the BRCA and Lynch genes have been well characterized, accurate risk assessment for pathogenic variants in more recently described genes may be complicated by factors which include small numbers of patients studied, potential ascertainment bias in the available studies, patients from only certain ethnic cohorts, low penetrance of pathogenic variants, wide confidence intervals in the results, and/or studies based on only one variant. Since the cancer risks are not yet well defined, no consensus guidelines for medical management may be available for these newer genes.

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Genetics:
Most genes on this panel are associated with an autosomal dominant cancer risk with the exception of *MUTYH* and *NTHL1*, which are 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.

Test Methods:
Genomic DNA is extracted from the submitted specimen. For skin punch biopsies, fibroblasts are cultured and used for DNA extraction. The DNA is enriched for the complete coding regions and splice 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, and for *APC*, promoters 1A and 1B 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 *CEBPA*, *PHOX2B*, *RET* and *SDHA*, only sequencing is performed. In addition, polyalanine repeats for the commonly expanded region in exon 3 of *PHOX2B* are not resolved. For *EPCAM* and *SCG5*, 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.

Clinical Sensitivity:
The clinical sensitivity of sequencing and deletion/duplication analysis of the 83 genes included in the OncoGeneDx Custom 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. Sensitivity for *NF2* is limited by somatic mosaicism; therefore, testing of tumor tissue may be considered after a negative result in an apparently *de novo* patient with a high clinical suspicion of NF2 syndrome.

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

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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.

References:

1. Probability of Developing or Dying of Cancer - Surveillance Research Program. https://surveillance.cancer.gov/devcan/.
2. Benusiglio, P. R. *et al.* Clinical implications of CTNNA1 germline mutations in asymptomatic carriers. *Gastric Cancer Off. J. Int. Gastric Cancer Assoc. Jpn. Gastric Cancer Assoc.* **22**, 899–903 (2019).
3. Clark, D. F. *et al.* Loss-of-function variants in CTNNA1 detected on multigene panel testing in individuals with gastric or breast cancer. *Genet. Med. Off. J. Am. Coll. Med. Genet.* **22**, 840–846 (2020).
4. Beckers, A., Aaltonen, L. A., Daly, A. F. & Karhu, A. Familial isolated pituitary adenomas (FIPA) and the pituitary adenoma predisposition due to mutations in the aryl hydrocarbon receptor interacting protein (AIP) gene. *Endocr. Rev.* **34**, 239–277 (2013).
5. Greengard, E. G. & Park, J. R. ALK-Related Neuroblastic Tumor Susceptibility. in *GeneReviews(®)* (eds. Pagon, R. A. et al.) (University of Washington, Seattle, 1993).
6. Noris, P. *et al.* ANKRD26-related thrombocytopenia and myeloid malignancies. *Blood* **122**, 1987–1989 (2013).
7. Pippucci, T. *et al.* Mutations in the 5' UTR of ANKRD26, the ankirin repeat domain 26 gene, cause an autosomal-dominant form of inherited thrombocytopenia, THC2. *Am. J. Hum. Genet.* **88**, 115–120 (2011).
8. Averina, M., Jensvoll, H., Strand, H. & Sovershaev, M. A novel ANKRD26 gene variant causing inherited thrombocytopenia in a family of Finnish origin: Another brick in the wall? *Thromb. Res.* **151**, 41–43 (2017).
9. Ferrari, S. *et al.* Spectrum of 5'UTR mutations in ANKRD26 gene in patients with inherited thrombocytopenia: c.-140C>G mutation is more frequent than expected. *Platelets* **28**, 621–624 (2017).
10. Jasperson, K. W. Genetic testing by cancer site: colon (polyposis syndromes). *Cancer J. Sudbury Mass* **18**, 328–333 (2012).
11. 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).
12. Leoz, M. L., Carballal, S., Moreira, L., Ocaña, T. & Balaguer, F. The genetic basis of familial adenomatous polyposis and its implications for clinical practice and risk management. *Appl. Clin. Genet.* **8**, 95–107 (2015).
13. Alkhouri, N., Franciosi, J. P. & Mamula, P. Familial adenomatous polyposis in children and adolescents. *J. Pediatr. Gastroenterol. Nutr.* **51**, 727–732 (2010).
14. 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).
15. Einarsdóttir, K. *et al.* Effect of ATM, CHEK2 and ERBB2 TAGSNPs and haplotypes on endometrial cancer risk. *Hum. Mol. Genet.* **16**, 154–164 (2007).
16. Renwick, A. *et al.* ATM mutations that cause ataxia-telangiectasia are breast cancer susceptibility alleles. *Nat. Genet.* **38**, 873–875 (2006).
17. Roberts, N. J. *et al.* ATM mutations in patients with hereditary pancreatic cancer. *Cancer Discov.* **2**, 41–46 (2012).
18. 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).
19. Thompson, D. *et al.* Cancer risks and mortality in heterozygous ATM mutation carriers. *J. Natl. Cancer Inst.* **97**, 813–822 (2005).
20. Marvin, M. L. *et al.* AXIN2-associated autosomal dominant ectodermal dysplasia and neoplastic syndrome. *Am. J. Med. Genet. A.* **155A**, 898–902 (2011).
21. Lammi, L. *et al.* Mutations in AXIN2 cause familial tooth agenesis and predispose to colorectal cancer. *Am. J. Hum. Genet.* **74**, 1043–1050 (2004).
22. Pilarski, R., Rai, K., Cebulla, C. & Abdel-Rahman, M. BAP1 Tumor Predisposition Syndrome. in *GeneReviews*® (eds. Adam, M. P. et al.) (University of Washington, Seattle, 1993).
23. Rai, K., Pilarski, R., Cebulla, C. M. & Abdel-Rahman, M. H. Comprehensive review of BAP1 tumor predisposition syndrome with report of two new cases. *Clin. Genet.* **89**, 285–294 (2016).
24. 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).
25. 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).

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26. 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).
27. Ratajska, M. *et al.* Cancer predisposing BARD1 mutations in breast-ovarian cancer families. *Breast Cancer Res. Treat.* **131**, 89–97 (2012).
28. Jasperson, K. W., Tuohy, T. M., Neklason, D. W. & Burt, R. W. Hereditary and familial colon cancer. *Gastroenterology* **138**, 2044–2058 (2010).
29. Rohlin, A. *et al.* Expanding the genotype-phenotype spectrum in hereditary colorectal cancer by gene panel testing. *Fam. Cancer* **16**, 195–203 (2017).
30. Brosens, L. A. A. *et al.* Risk of colorectal cancer in juvenile polyposis. *Gut* **56**, 965–967 (2007).
31. 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).
32. 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).
33. 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).
34. Chen, S. & Parmigiani, G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **25**, 1329–1333 (2007).
35. 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).
36. 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).
37. 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).
38. 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).
39. Pennington, K. P. *et al.* BRCA1, TP53, and CHEK2 germline mutations in uterine serous carcinoma. *Cancer* **119**, 332–338 (2013).
40. 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).
41. 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).
42. 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).
43. Pritchard, C. C. *et al.* Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. *N. Engl. J. Med.* **375**, 443–453 (2016).
44. Ghazwani, Y. *et al.* Clinical characteristics and genetic subtypes of Fanconi anemia in Saudi patients. *Cancer Genet.* **209**, 171–176 (2016).
45. Jackson, M. A., Rich, T. A., Hu, M. I., Perrier, N. D. & Waguespack, S. G. CDC73-Related Disorders. in *GeneReviews(®)* (eds. Pagon, R. A. et al.) (University of Washington, Seattle, 1993).
46. 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).
47. Kaurah, P. *et al.* Founder and recurrent CDH1 mutations in families with hereditary diffuse gastric cancer. *JAMA* **297**, 2360–2372 (2007).
48. Petridis, C. *et al.* Germline CDH1 mutations in bilateral lobular carcinoma in situ. *Br. J. Cancer* **110**, 1053–1057 (2014).
49. 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).
50. 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).
51. 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).
52. Guilford, P. *et al.* E-cadherin germline mutations in familial gastric cancer. *Nature* **392**, 402–405 (1998).
53. Leachman, S. A. *et al.* Identification, genetic testing, and management of hereditary melanoma. *Cancer Metastasis Rev.* **36**, 77–90 (2017).
54. Goldstein, A. M. *et al.* High-risk melanoma susceptibility genes and pancreatic cancer, neural system tumors, and uveal melanoma across GenoMEL. *Cancer Res.* **66**, 9818–9828 (2006).
55. Puntervoll, H. E. *et al.* Melanoma prone families with CDK4 germline mutation: phenotypic profile and associations with MC1R variants. *J. Med. Genet.* **50**, 264–270 (2013).
56. Alrezk, R., Hannah-Shmouni, F. & Stratakis, C. A. MEN4 and CDKN1B mutations: the latest of the MEN syndromes. *Endocr. Relat. Cancer* **24**, T195–T208 (2017).
57. Goldstein, A. M. *et al.* Features associated with germline CDKN2A mutations: a GenoMEL study of melanoma-prone families from three continents. *J. Med. Genet.* **44**, 99–106 (2007).
58. Kefford, R. F., Newton Bishop, J. A., Bergman, W. & Tucker, M. A. Counseling and DNA testing for individuals perceived to be genetically predisposed to melanoma: A consensus statement of the Melanoma Genetics Consortium. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **17**, 3245–3251 (1999).
59. Czajkowski, R., Placek, W., Drewa, G., Czajkowska, A. & Uchańska, G. FAMMM syndrome: pathogenesis and management. *Dermatol. Surg. Off. Publ. Am. Soc. Dermatol. Surg. Al* **30**, 291–296 (2004).
60. Canto, M. I. *et al.* International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut* **62**, 339–347 (2013).
61. Soura, E., Eliades, P. J., Shannon, K., Stratigos, A. J. & Tsao, H. Hereditary melanoma: Update on syndromes and management: Emerging melanoma cancer complexes and genetic counseling. *J. Am. Acad. Dermatol.* **74**, 411–420; quiz 421–422 (2016).
62. Tawana, K. & Fitzgibbon, J. CEBPA-Associated Familial Acute Myeloid Leukemia (AML). in *GeneReviews*® (eds. Adam, M. P. et al.) (University of Washington, Seattle, 1993).
63. Tawana, K. *et al.* Disease evolution and outcomes in familial AML with germline CEBPA mutations. *Blood* **126**, 1214–1223 (2015).
64. Cybulski, C. *et al.* CHEK2 is a multiorgan cancer susceptibility gene. *Am. J. Hum. Genet.* **75**, 1131–1135 (2004).

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65. Dong, X. *et al.* Mutations in CHEK2 associated with prostate cancer risk. *Am. J. Hum. Genet.* **72**, 270–280 (2003).
66. 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).
67. 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).
68. 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).
69. Seppälä, E. H. *et al.* CHEK2 variants associate with hereditary prostate cancer. *Br. J. Cancer* **89**, 1966–1970 (2003).
70. Suchy, J. *et al.* CHEK2 mutations and HNPCC-related colorectal cancer. *Int. J. Cancer* **126**, 3005–3009 (2010).
71. Cardoso, S. R. *et al.* Germline heterozygous DDX41 variants in a subset of familial myelodysplasia and acute myeloid leukemia. *Leukemia* **30**, 2083–2086 (2016).
72. Lewinsohn, M. *et al.* Novel germ line DDX41 mutations define families with a lower age of MDS/AML onset and lymphoid malignancies. *Blood* **127**, 1017–1023 (2016).
73. Li, R., Sobreira, N., Witmer, P. D., Pratz, K. W. & Braunstein, E. M. Two novel germline DDX41 mutations in a family with inherited myelodysplasia/acute myeloid leukemia. *Haematologica* **101**, e228-231 (2016).
74. Doros, L. *et al.* DICER1-Related Disorders. in *GeneReviews(®)* (eds. Pagon, R. A. et al.) (University of Washington, Seattle, 1993).
75. Foulkes, W. D. *et al.* Extending the phenotypes associated with DICER1 mutations. *Hum. Mutat.* **32**, 1381–1384 (2011).
76. 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).
77. 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).
78. 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).
79. Vasen, H. F. *et al.* Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. *Gastroenterology* **110**, 1020–1027 (1996).
80. Wimmer, K. & Kratz, C. P. Constitutional mismatch repair-deficiency syndrome. *Haematologica* **95**, 699–701 (2010).
81. 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).
82. Feurstein, S. & Godley, L. A. Germline ETV6 mutations and predisposition to hematological malignancies. *Int. J. Hematol.* **106**, 189–195 (2017).
83. Dirse, V. *et al.* ETV6 and NOTCH1 germline variants in adult acute leukemia. *Leuk. Lymphoma* **59**, 1022–1024 (2018).
84. Berwick, M. *et al.* Genetic heterogeneity among Fanconi anemia heterozygotes and risk of cancer. *Cancer Res.* **67**, 9591–9596 (2007).
85. 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).
86. 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).
87. 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).
88. 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).
89. Menko, F. H. *et al.* Hereditary leiomyomatosis and renal cell cancer (HLRCC): renal cancer risk, surveillance and treatment. *Fam. Cancer* **13**, 637–644 (2014).
90. Smit, D. L. *et al.* Hereditary leiomyomatosis and renal cell cancer in families referred for fumarate hydratase germline mutation analysis. *Clin. Genet.* **79**, 49–59 (2011).
91. Home - HLRCC Family Alliance. http://hlrccinfo.org/.
92. Pithukpakorn, M. & Toro, J. R. Hereditary Leiomyomatosis and Renal Cell Cancer. in *GeneReviews(®)* (eds. Pagon, R. A. et al.) (University of Washington, Seattle, 1993).
93. Coughlin, E. M. *et al.* Molecular analysis and prenatal diagnosis of human fumarase deficiency. *Mol. Genet. Metab.* **63**, 254–262 (1998).
94. Menko, F. H. *et al.* Birt-Hogg-Dubé syndrome: diagnosis and management. *Lancet Oncol.* **10**, 1199–1206 (2009).
95. Schmidt, L. S. *et al.* Germline BHD-mutation spectrum and phenotype analysis of a large cohort of families with Birt-Hogg-Dubé syndrome. *Am. J. Hum. Genet.* **76**, 1023–1033 (2005).
96. Toro, J. R. Birt-Hogg-Dubé Syndrome. in *GeneReviews(®)* (eds. Pagon, R. A. et al.) (University of Washington, Seattle, 1993).
97. Toro, J. R. *et al.* BHD mutations, clinical and molecular genetic investigations of Birt-Hogg-Dubé syndrome: a new series of 50 families and a review of published reports. *J. Med. Genet.* **45**, 321–331 (2008).
98. Benusiglio, P. R. *et al.* Renal cell tumour characteristics in patients with the Birt-Hogg-Dubé cancer susceptibility syndrome: a retrospective, multicentre study. *Orphanet J. Rare Dis.* **9**, 163 (2014).
99. Hsu, A. P. *et al.* Mutations in GATA2 are associated with the autosomal dominant and sporadic monocytopenia and mycobacterial infection (MonoMAC) syndrome. *Blood* **118**, 2653–2655 (2011).
100. Ostergaard, P. *et al.* Mutations in GATA2 cause primary lymphedema associated with a predisposition to acute myeloid leukemia (Emberger syndrome). *Nat. Genet.* **43**, 929–931 (2011).
101. Spinner, M. A. *et al.* GATA2 deficiency: a protean disorder of hematopoiesis, lymphatics, and immunity. *Blood* **123**, 809–821 (2014).
102. Kazenwadel, J. *et al.* Loss-of-function germline GATA2 mutations in patients with MDS/AML or MonoMAC syndrome and primary lymphedema reveal a key role for GATA2 in the lymphatic vasculature. *Blood* **119**, 1283–1291 (2012).
103. Wlodarski, M. W. *et al.* Prevalence, clinical characteristics, and prognosis of GATA2-related myelodysplastic syndromes in children and adolescents. *Blood* **127**, 1387–1397; quiz 1518 (2016).
104. Ewing, C. M. *et al.* Germline mutations in HOXB13 and prostate-cancer risk. *N. Engl. J. Med.* **366**, 141–149 (2012).
105. Akbari, M. R. *et al.* Association between germline HOXB13 G84E mutation and risk of prostate cancer. *J. Natl. Cancer Inst.* **104**, 1260–1262 (2012).
106. Alanee, S., Couch, F. & Offit, K. Association of a HOXB13 variant with breast cancer. *N. Engl. J. Med.* **367**, 480–481 (2012).

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107. Bachet, J.-B. *et al.* Diagnosis, prognosis and treatment of patients with gastrointestinal stromal tumour (GIST) and germline mutation of KIT exon 13. *Eur. J. Cancer Oxf. Engl. 1990* **49**, 2531–2541 (2013).
108. Farag, S. *et al.* Remarkable effects of imatinib in a family with young onset gastrointestinal stromal tumors and cutaneous hyperpigmentation associated with a germline KIT-Trp557Arg mutation: case report and literature overview. *Fam. Cancer* **17**, 247–253 (2018).
109. Ke, H., Kazi, J. U., Zhao, H. & Sun, J. Germline mutations of KIT in gastrointestinal stromal tumor (GIST) and mastocytosis. *Cell Biosci.* **6**, 55 (2016).
110. Dhamija, R., Plotkin, S., Asthagiri, A., Messiaen, L. & Babovic-Vuksanovic, D. Schwannomatosis. in *GeneReviews®* (eds. Adam, M. P. et al.) (University of Washington, Seattle, 1993).
111. Allanson, J. E. & Roberts, A. E. Noonan Syndrome. in *GeneReviews®* (eds. Adam, M. P. et al.) (University of Washington, Seattle, 1993).
112. Kehrer-Sawatzki, H., Farschtschi, S., Mautner, V.-F. & Cooper, D. N. The molecular pathogenesis of schwannomatosis, a paradigm for the co-involvement of multiple tumour suppressor genes in tumorigenesis. *Hum. Genet.* **136**, 129–148 (2017).
113. Lenders, J. W. M. *et al.* Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J. Clin. Endocrinol. Metab.* **99**, 1915–1942 (2014).
114. Comino-Méndez, I. *et al.* Exome sequencing identifies MAX mutations as a cause of hereditary pheochromocytoma. *Nat. Genet.* **43**, 663–667 (2011).
115. Burnichon, N. *et al.* MAX mutations cause hereditary and sporadic pheochromocytoma and paraganglioma. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **18**, 2828–2837 (2012).
116. Martins, R. & Bugalho, M. J. Paragangliomas/Pheochromocytomas: clinically oriented genetic testing. *Int. J. Endocrinol.* **2014**, 794187 (2014).
117. Bausch, B. *et al.* Clinical Characterization of the Pheochromocytoma and Paraganglioma Susceptibility Genes SDHA, TMEM127, MAX, and SDHAF2 for Gene-Informed Prevention. *JAMA Oncol.* **3**, 1204–1212 (2017).
118. Thakker, R. V. *et al.* Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J. Clin. Endocrinol. Metab.* **97**, 2990–3011 (2012).
119. Bassett, J. H. *et al.* Characterization of mutations in patients with multiple endocrine neoplasia type 1. *Am. J. Hum. Genet.* **62**, 232–244 (1998).
120. Brandi, M. L. *et al.* Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J. Clin. Endocrinol. Metab.* **86**, 5658–5671 (2001).
121. Giusti, F., Marini, F. & Brandi, M. L. Multiple Endocrine Neoplasia Type 1. in *GeneReviews(®)* (eds. Pagon, R. A. et al.) (University of Washington, Seattle, 1993).
122. Giusti, F. *et al.* Multiple endocrine neoplasia syndrome type 1: institution, management, and data analysis of a nationwide multicenter patient database. *Endocrine* **58**, 349–359 (2017).
123. Olivero, M. *et al.* Novel mutation in the ATP-binding site of the MET oncogene tyrosine kinase in a HPRCC family. *Int. J. Cancer* **82**, 640–643 (1999).
124. Lubensky, I. A. *et al.* Hereditary and sporadic papillary renal carcinomas with c-met mutations share a distinct morphological phenotype. *Am. J. Pathol.* **155**, 517–526 (1999).
125. Ornstein, D. K. *et al.* Prevalence of microscopic tumors in normal appearing renal parenchyma of patients with hereditary papillary renal cancer. *J. Urol.* **163**, 431–433 (2000).
126. Schmidt, L. S. *et al.* Early onset hereditary papillary renal carcinoma: germline missense mutations in the tyrosine kinase domain of the met proto-oncogene. *J. Urol.* **172**, 1256–1261 (2004).
127. Bertolotto, C. *et al.* A SUMOylation-defective MITF germline mutation predisposes to melanoma and renal carcinoma. *Nature* **480**, 94–98 (2011).
128. Ghiorzo, P. *et al.* Prevalence of the E318K MITF germline mutation in Italian melanoma patients: associations with histological subtypes and family cancer history. *Pigment Cell Melanoma Res.* **26**, 259–262 (2013).
129. Potrony, M. *et al.* Prevalence of MITF p.E318K in Patients With Melanoma Independent of the Presence of CDKN2A Causative Mutations. *JAMA Dermatol.* **152**, 405–412 (2016).
130. Bonadona, V. *et al.* Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA* **305**, 2304–2310 (2011).
131. 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).
132. Baglietto, L. *et al.* Risks of Lynch syndrome cancers for MSH6 mutation carriers. *J. Natl. Cancer Inst.* **102**, 193–201 (2010).
133. 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).
134. 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).
135. Boparai, K. S. *et al.* Hyperplastic polyps and sessile serrated adenomas as a phenotypic expression of MYH-associated polyposis. *Gastroenterology* **135**, 2014–2018 (2008).
136. 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).
137. 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).
138. 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).
139. 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).
140. 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).
141. Vogt, S. *et al.* Expanded extracolonic tumor spectrum in MUTYH-associated polyposis. *Gastroenterology* **137**, 1976-1985.e1–10 (2009).
142. 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).

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143. Cleary, S. P. *et al.* Germline MutY human homologue mutations and colorectal cancer: a multisite case-control study. *Gastroenterology* **136**, 1251–1260 (2009).
144. 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).
145. Steffen, J. *et al.* Increased cancer risk of heterozygotes with NBS1 germline mutations in Poland. *Int. J. Cancer* **111**, 67–71 (2004).
146. 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).
147. 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).
148. 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).
149. di Masi, A. & Antoccia, A. NBS1 Heterozygosity and Cancer Risk. *Curr. Genomics* **9**, 275–281 (2008).
150. 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).
151. Friedman, J. M. Neurofibromatosis 1. in *GeneReviews(®)* (eds. Pagon, R. A. et al.) (University of Washington, Seattle, 1993).
152. Ferner, R. E. & Gutmann, D. H. Neurofibromatosis type 1 (NF1): diagnosis and management. *Handb. Clin. Neurol.* **115**, 939–955 (2013).
153. Ferner, R. E. *et al.* Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. *J. Med. Genet.* **44**, 81–88 (2007).
154. Evans, D. G., Raymond, F. L., Barwell, J. G. & Halliday, D. Genetic testing and screening of individuals at risk of NF2. *Clin. Genet.* **82**, 416–424 (2012).
155. Evans, D. G. R. *et al.* Cancer and Central Nervous System Tumor Surveillance in Pediatric Neurofibromatosis 2 and Related Disorders. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **23**, e54–e61 (2017).
156. Evans, D. G., Birch, J. M. & Ramsden, R. T. Paediatric presentation of type 2 neurofibromatosis. *Arch. Dis. Child.* **81**, 496–499 (1999).
157. Asthagiri, A. R. *et al.* Neurofibromatosis type 2. *Lancet Lond. Engl.* **373**, 1974–1986 (2009).
158. Weren, R. D. A. *et al.* A germline homozygous mutation in the base-excision repair gene NTHL1 causes adenomatous polyposis and colorectal cancer. *Nat. Genet.* **47**, 668–671 (2015).
159. Rivera, B., Castellsagué, E., Bah, I., van Kempen, L. C. & Foulkes, W. D. Biallelic NTHL1 Mutations in a Woman with Multiple Primary Tumors. *N. Engl. J. Med.* **373**, 1985–1986 (2015).
160. Belhadj, S. *et al.* Delineating the Phenotypic Spectrum of the NTHL1-Associated Polyposis. *Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc.* **15**, 461–462 (2017).
161. Broderick, P. *et al.* Validation of Recently Proposed Colorectal Cancer Susceptibility Gene Variants in an Analysis of Families and Patients-a Systematic Review. *Gastroenterology* **152**, 75-77.e4 (2017).
162. Rahman, N. *et al.* PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. *Nat. Genet.* **39**, 165–167 (2007).
163. Erkko, H. *et al.* A recurrent mutation in PALB2 in Finnish cancer families. *Nature* **446**, 316–319 (2007).
164. Antoniou, A. C. *et al.* Breast-cancer risk in families with mutations in PALB2. *N. Engl. J. Med.* **371**, 497–506 (2014).
165. Casadei, S. *et al.* Contribution of inherited mutations in the BRCA2-interacting protein PALB2 to familial breast cancer. *Cancer Res.* **71**, 2222–2229 (2011).
166. Jones, S. *et al.* Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. *Science* **324**, 217 (2009).
167. Slater, E. P. *et al.* PALB2 mutations in European familial pancreatic cancer families. *Clin. Genet.* **78**, 490–494 (2010).
168. Carney, J. A. & Stratakis, C. A. Stromal, fibrous, and fatty gastrointestinal tumors in a patient with a PDGFRA gene mutation. *Am. J. Surg. Pathol.* **32**, 1412–1420 (2008).
169. Chompret, A. *et al.* PDGFRA germline mutation in a family with multiple cases of gastrointestinal stromal tumor. *Gastroenterology* **126**, 318–321 (2004).
170. Ricci, R. *et al.* PDGFRA-mutant syndrome. *Mod. Pathol. Off. J. U. S. Can. Acad. Pathol. Inc* **28**, 954–964 (2015).
171. Weese-Mayer, D. E. *et al.* An official ATS clinical policy statement: Congenital central hypoventilation syndrome: genetic basis, diagnosis, and management. *Am. J. Respir. Crit. Care Med.* **181**, 626–644 (2010).
172. Weese-Mayer, D. E., Marazita, M. L., Rand, C. M. & Berry-Kravis, E. M. Congenital Central Hypoventilation Syndrome. in *GeneReviews(®)* (eds. Pagon, R. A. et al.) (University of Washington, Seattle, 1993).
173. Weese-Mayer, D. E. *et al.* Idiopathic congenital central hypoventilation syndrome: analysis of genes pertinent to early autonomic nervous system embryologic development and identification of mutations in PHOX2b. *Am. J. Med. Genet. A.* **123A**, 267–278 (2003).
174. Trochet, D. *et al.* PHOX2B genotype allows for prediction of tumor risk in congenital central hypoventilation syndrome. *Am. J. Hum. Genet.* **76**, 421–426 (2005).
175. Senter, L. *et al.* The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. *Gastroenterology* **135**, 419–428 (2008).
176. 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).
177. 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).
178. 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).
179. Spier, I. *et al.* Frequency and phenotypic spectrum of germline mutations in POLE and seven other polymerase genes in 266 patients with colorectal adenomas and carcinomas. *Int. J. Cancer* **137**, 320–331 (2015).
180. Wimmer, K. *et al.* A novel germline POLE mutation causes an early onset cancer prone syndrome mimicking constitutional mismatch repair deficiency. *Fam. Cancer* **16**, 67–71 (2017).
181. Pachlopnik Schmid, J. *et al.* Polymerase ε1 mutation in a human syndrome with facial dysmorphism, immunodeficiency, livedo, and short stature ('FILS syndrome'). *J. Exp. Med.* **209**, 2323–2330 (2012).
182. Shi, J. *et al.* Rare missense variants in POT1 predispose to familial cutaneous malignant melanoma. *Nat. Genet.* **46**, 482–486 (2014).
183. Robles-Espinoza, C. D. *et al.* POT1 loss-of-function variants predispose to familial melanoma. *Nat. Genet.* **46**, 478–481 (2014).
184. Wilson, T. L.-S. *et al.* A new POT1 germline mutation-expanding the spectrum of POT1-associated cancers. *Fam. Cancer* (2017) doi:10.1007/s10689-017-9984-y.

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185. Calvete, O. *et al.* A mutation in the POT1 gene is responsible for cardiac angiosarcoma in TP53-negative Li-Fraumeni-like families. *Nat. Commun.* **6**, 8383 (2015).
186. Bainbridge, M. N. *et al.* Germline mutations in shelterin complex genes are associated with familial glioma. *J. Natl. Cancer Inst.* **107**, 384 (2015).
187. Speedy, H. E. *et al.* Germ line mutations in shelterin complex genes are associated with familial chronic lymphocytic leukemia. *Blood* **128**, 2319–2326 (2016).
188. Stratakis, C. A. Carney complex: A familial lentiginosis predisposing to a variety of tumors. *Rev. Endocr. Metab. Disord.* **17**, 367–371 (2016).
189. Stratakis, C. A., Salpea, P. & Raygada, M. Carney Complex. in *GeneReviews(®)* (eds. Pagon, R. A. et al.) (University of Washington, Seattle, 1993).
190. Stratakis, C. A., Kirschner, L. S. & Carney, J. A. Clinical and molecular features of the Carney complex: diagnostic criteria and recommendations for patient evaluation. *J. Clin. Endocrinol. Metab.* **86**, 4041–4046 (2001).
191. Correa, R., Salpea, P. & Stratakis, C. A. Carney complex: an update. *Eur. J. Endocrinol.* **173**, M85-97 (2015).
192. Bree, A. F., Shah, M. R., & BCNS Colloquium Group. Consensus statement from the first international colloquium on basal cell nevus syndrome (BCNS). *Am. J. Med. Genet. A.* **155A**, 2091–2097 (2011).
193. Evans, D. G. & Farndon, P. A. Nevoid Basal Cell Carcinoma Syndrome. in *GeneReviews(®)* (eds. Pagon, R. A. et al.) (University of Washington, Seattle, 1993).
194. Foulkes, W. D. *et al.* Cancer Surveillance in Gorlin Syndrome and Rhabdoid Tumor Predisposition Syndrome. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **23**, e62–e67 (2017).
195. Bubien, V. *et al.* High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome. *J. Med. Genet.* **50**, 255–263 (2013).
196. Hobert, J. A. & Eng, C. PTEN hamartoma tumor syndrome: an overview. *Genet. Med. Off. J. Am. Coll. Med. Genet.* **11**, 687–694 (2009).
197. Nieuwenhuis, M. H. *et al.* Cancer risk and genotype-phenotype correlations in PTEN hamartoma tumor syndrome. *Fam. Cancer* **13**, 57–63 (2014).
198. 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).
199. Norquist, B. M. *et al.* Inherited Mutations in Women With Ovarian Carcinoma. *JAMA Oncol.* **2**, 482–490 (2016).
200. 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).
201. Couch, F. J. *et al.* Associations Between Cancer Predisposition Testing Panel Genes and Breast Cancer. *JAMA Oncol.* **3**, 1190–1196 (2017).
202. 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).
203. Loveday, C. *et al.* Germline mutations in RAD51D confer susceptibility to ovarian cancer. *Nat. Genet.* **43**, 879–882 (2011).
204. 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).
205. Lohmann, D. R. & Gallie, B. L. Retinoblastoma. in *GeneReviews(®)* (eds. Pagon, R. A. et al.) (University of Washington, Seattle, 1993).
206. de Jong, M. C. *et al.* Trilateral retinoblastoma: a systematic review and meta-analysis. *Lancet Oncol.* **15**, 1157–1167 (2014).
207. Dimaras, H. *et al.* Loss of RB1 induces non-proliferative retinoma: increasing genomic instability correlates with progression to retinoblastoma. *Hum. Mol. Genet.* **17**, 1363–1372 (2008).
208. Marees, T. *et al.* Risk of second malignancies in survivors of retinoblastoma: more than 40 years of follow-up. *J. Natl. Cancer Inst.* **100**, 1771–1779 (2008).
209. Kleinerman, R. A. *et al.* Risk of soft tissue sarcomas by individual subtype in survivors of hereditary retinoblastoma. *J. Natl. Cancer Inst.* **99**, 24–31 (2007).
210. Sun, J. *et al.* Mutations in RECQL Gene Are Associated with Predisposition to Breast Cancer. *PLoS Genet.* **11**, e1005228 (2015).
211. Cybulski, C. *et al.* Germline RECQL mutations are associated with breast cancer susceptibility. *Nat. Genet.* **47**, 643–646 (2015).
212. Akbari, M. R. & Cybulski, C. RECQL: a DNA helicase in breast cancer. *Oncotarget* **6**, 26558–26559 (2015).
213. Kwong, A. *et al.* Germline RECQL mutations in high risk Chinese breast cancer patients. *Breast Cancer Res. Treat.* **157**, 211–215 (2016).
214. American Thyroid Association Guidelines Task Force *et al.* Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid Off. J. Am. Thyroid Assoc.* **19**, 565–612 (2009).
215. Marquard, J. & Eng, C. Multiple Endocrine Neoplasia Type 2. in *GeneReviews*® (eds. Adam, M. P. et al.) (University of Washington, Seattle, 1993).
216. Romei, C. *et al.* Twenty years of lesson learning: how does the RET genetic screening test impact the clinical management of medullary thyroid cancer? *Clin. Endocrinol. (Oxf.)* **82**, 892–899 (2015).
217. Latger-Cannard, V. *et al.* Haematological spectrum and genotype-phenotype correlations in nine unrelated families with RUNX1 mutations from the French network on inherited platelet disorders. *Orphanet J. Rare Dis.* **11**, 49 (2016).
218. Liew, E. & Owen, C. Familial myelodysplastic syndromes: a review of the literature. *Haematologica* **96**, 1536–1542 (2011).
219. Owen, C. J. *et al.* Five new pedigrees with inherited RUNX1 mutations causing familial platelet disorder with propensity to myeloid malignancy. *Blood* **112**, 4639–4645 (2008).
220. Preudhomme, C. *et al.* High frequency of RUNX1 biallelic alteration in acute myeloid leukemia secondary to familial platelet disorder. *Blood* **113**, 5583–5587 (2009).
221. Topaz, O. *et al.* A deleterious mutation in SAMD9 causes normophosphatemic familial tumoral calcinosis. *Am. J. Hum. Genet.* **79**, 759–764 (2006).
222. Chefetz, I. *et al.* Normophosphatemic familial tumoral calcinosis is caused by deleterious mutations in SAMD9, encoding a TNF-alpha responsive protein. *J. Invest. Dermatol.* **128**, 1423–1429 (2008).
223. Jeffries, L. *et al.* A novel SAMD9 mutation causing MIRAGE syndrome: An expansion and review of phenotype, dysmorphology, and natural history. *Am. J. Med. Genet. A.* **176**, 415–420 (2018).
224. Narumi, S. *et al.* SAMD9 mutations cause a novel multisystem disorder, MIRAGE syndrome, and are associated with loss of chromosome 7. *Nat. Genet.* **48**, 792–797 (2016).
225. Nagata, Y. *et al.* Germline loss-of-function SAMD9 and SAMD9L alterations in adult myelodysplastic syndromes. *Blood* **132**, 2309–2313 (2018).

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226. Davidsson, J. *et al.* SAMD9 and SAMD9L in inherited predisposition to ataxia, pancytopenia, and myeloid malignancies. *Leukemia* **32**, 1106–1115 (2018).
227. Phowthongkum, P., Chen, D.-H., Raskind, W. H. & Bird, T. SAMD9L-Related Ataxia-Pancytopenia Syndrome. in *GeneReviews®* (eds. Adam, M. P. et al.) (University of Washington, Seattle, 1993).
228. Thunström, S. & Axelsson, M. Leukoencephalopathia, demyelinating peripheral neuropathy and dural ectasia explained by a not formerly described de novo mutation in the SAMD9L gene, ends 27 years of investigations - a case report. *BMC Neurol.* **19**, 89 (2019).
229. Rohlin, A. *et al.* GREM1 and POLE variants in hereditary colorectal cancer syndromes. *Genes. Chromosomes Cancer* **55**, 95–106 (2016).
230. Jaeger, E. *et al.* Hereditary mixed polyposis syndrome is caused by a 40-kb upstream duplication that leads to increased and ectopic expression of the BMP antagonist GREM1. *Nat. Genet.* **44**, 699–703 (2012).
231. Lieberman, S. *et al.* Features of Patients With Hereditary Mixed Polyposis Syndrome Caused by Duplication of GREM1 and Implications for Screening and Surveillance. *Gastroenterology* **152**, 1876-1880.e1 (2017).
232. Kirmani, S. & Young, W. F. Hereditary Paraganglioma-Pheochromocytoma Syndromes. in *GeneReviews(®)* (eds. Pagon, R. A. et al.) (University of Washington, Seattle, 1993).
233. Helman, G. *et al.* Magnetic resonance imaging spectrum of succinate dehydrogenase-related infantile leukoencephalopathy. *Ann. Neurol.* **79**, 379–386 (2016).
234. Korpershoek, E. *et al.* SDHA immunohistochemistry detects germline SDHA gene mutations in apparently sporadic paragangliomas and pheochromocytomas. *J. Clin. Endocrinol. Metab.* **96**, E1472-1476 (2011).
235. Burnichon, N. *et al.* SDHA is a tumor suppressor gene causing paraganglioma. *Hum. Mol. Genet.* **19**, 3011–3020 (2010).
236. Kunst, H. P. M. *et al.* SDHAF2 (PGL2-SDH5) and hereditary head and neck paraganglioma. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **17**, 247–254 (2011).
237. Neumann, H. P. H. *et al.* Distinct clinical features of paraganglioma syndromes associated with SDHB and SDHD gene mutations. *JAMA* **292**, 943–951 (2004).
238. Welander, J., Söderkvist, P. & Gimm, O. Genetics and clinical characteristics of hereditary pheochromocytomas and paragangliomas. *Endocr. Relat. Cancer* **18**, R253-276 (2011).
239. Niemann, S. & Müller, U. Mutations in SDHC cause autosomal dominant paraganglioma, type 3. *Nat. Genet.* **26**, 268–270 (2000).
240. Peczkowska, M. *et al.* Extra-adrenal and adrenal pheochromocytomas associated with a germline SDHC mutation. *Nat. Clin. Pract. Endocrinol. Metab.* **4**, 111–115 (2008).
241. Miettinen, M. & Lasota, J. Succinate dehydrogenase deficient gastrointestinal stromal tumors (GISTs) - a review. *Int. J. Biochem. Cell Biol.* **53**, 514–519 (2014).
242. Benn, D. E. *et al.* Clinical presentation and penetrance of pheochromocytoma/paraganglioma syndromes. *J. Clin. Endocrinol. Metab.* **91**, 827–836 (2006).
243. Jackson, C. B. *et al.* Mutations in SDHD lead to autosomal recessive encephalomyopathy and isolated mitochondrial complex II deficiency. *J. Med. Genet.* **51**, 170–175 (2014).
244. Jasperson, K. & Burt, R. W. The Genetics of Colorectal Cancer. *Surg. Oncol. Clin. N. Am.* **24**, 683–703 (2015).
245. Howe, J. R., Mitros, F. A. & Summers, R. W. The risk of gastrointestinal carcinoma in familial juvenile polyposis. *Ann. Surg. Oncol.* **5**, 751–756 (1998).
246. Schrier Vergano, S. *et al.* Coffin-Siris Syndrome. in *GeneReviews®* (eds. Adam, M. P. et al.) (University of Washington, Seattle, 1993).
247. Hasselblatt, M. *et al.* SMARCA4-mutated atypical teratoid/rhabdoid tumors are associated with inherited germline alterations and poor prognosis. *Acta Neuropathol. (Berl.)* **128**, 453–456 (2014).
248. Witkowski, L. *et al.* The influence of clinical and genetic factors on patient outcome in small cell carcinoma of the ovary, hypercalcemic type. *Gynecol. Oncol.* **141**, 454–460 (2016).
249. Berchuck, A., Witkowski, L., Hasselblatt, M. & Foulkes, W. D. Prophylactic oophorectomy for hereditary small cell carcinoma of the ovary, hypercalcemic type. *Gynecol. Oncol. Rep.* **12**, 20–22 (2015).
250. Foulkes, W. D., Gore, M. & McCluggage, W. G. Rare non-epithelial ovarian neoplasms: Pathology, genetics and treatment. *Gynecol. Oncol.* **142**, 190–198 (2016).
251. Teplick, A., Kowalski, M., Biegel, J. A. & Nichols, K. E. Educational paper: screening in cancer predisposition syndromes: guidelines for the general pediatrician. *Eur. J. Pediatr.* **170**, 285–294 (2011).
252. Smith, M. J. Germline and somatic mutations in meningiomas. *Cancer Genet.* **208**, 107–114 (2015).
253. Sredni, S. T. & Tomita, T. Rhabdoid tumor predisposition syndrome. *Pediatr. Dev. Pathol. Off. J. Soc. Pediatr. Pathol. Paediatr. Pathol. Soc.* **18**, 49–58 (2015).
254. Kehrer-Sawatzki, H., Farschtschi, S., Mautner, V.-F. & Cooper, D. N. The molecular pathogenesis of schwannomatosis, a paradigm for the co-involvement of multiple tumour suppressor genes in tumorigenesis. *Hum. Genet.* **136**, 129–148 (2017).
255. Smith, M. J. *et al.* Germline SMARCE1 mutations predispose to both spinal and cranial clear cell meningiomas. *J. Pathol.* **234**, 436–440 (2014).
256. Smith, M. J. *et al.* Loss-of-function mutations in SMARCE1 cause an inherited disorder of multiple spinal meningiomas. *Nat. Genet.* **45**, 295–298 (2013).
257. Gerkes, E. H. *et al.* A heritable form of SMARCE1-related meningiomas with important implications for follow-up and family screening. *Neurogenetics* **17**, 83–89 (2016).
258. Smith, M. J. *et al.* SMARCE1 mutation screening in classification of clear cell meningiomas. *Histopathology* **70**, 814–820 (2017).
259. Kirwan, M. *et al.* Exome sequencing identifies autosomal-dominant SRP72 mutations associated with familial aplasia and myelodysplasia. *Am. J. Hum. Genet.* **90**, 888–892 (2012).
260. Tomlinson, I. P. & Houlston, R. S. Peutz-Jeghers syndrome. *J. Med. Genet.* **34**, 1007–1011 (1997).
261. Hearle, N. *et al.* Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **12**, 3209–3215 (2006).
262. Giardiello, F. M. *et al.* Very high risk of cancer in familial Peutz-Jeghers syndrome. *Gastroenterology* **119**, 1447–1453 (2000).
263. Taylor, M. D. *et al.* Mutations in SUFU predispose to medulloblastoma. *Nat. Genet.* **31**, 306–310 (2002).
264. Smith, M. J. *et al.* Germline mutations in SUFU cause Gorlin syndrome-associated childhood medulloblastoma and redefine the risk associated with PTCH1 mutations. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **32**, 4155–4161 (2014).
265. Savage, S. A. Dyskeratosis Congenita. in *GeneReviews®* (eds. Adam, M. P. et al.) (University of Washington, Seattle, 1993).

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266. Yamaguchi, H. *et al.* Mutations of the human telomerase RNA gene (TERC) in aplastic anemia and myelodysplastic syndrome. *Blood* **102**, 916–918 (2003).
267. Savage, S. A. & Bertuch, A. A. The genetics and clinical manifestations of telomere biology disorders. *Genet. Med. Off. J. Am. Coll. Med. Genet.* **12**, 753–764 (2010).
268. Bessler, M., Du, H.-Y., Gu, B. & Mason, P. J. Dysfunctional telomeres and dyskeratosis congenita. *Haematologica* **92**, 1009–1012 (2007).
269. Vulliamy, T. *et al.* Disease anticipation is associated with progressive telomere shortening in families with dyskeratosis congenita due to mutations in TERC. *Nat. Genet.* **36**, 447–449 (2004).
270. Bessler, M., Wilson, D. B. & Mason, P. J. Dyskeratosis congenita. *FEBS Lett.* **584**, 3831–3838 (2010).
271. Du, H.-Y. *et al.* TERC and TERT gene mutations in patients with bone marrow failure and the significance of telomere length measurements. *Blood* **113**, 309–316 (2009).
272. Yamaguchi, H. *et al.* Mutations in TERT, the gene for telomerase reverse transcriptase, in aplastic anemia. *N. Engl. J. Med.* **352**, 1413–1424 (2005).
273. Basel-Vanagaite, L. *et al.* Expanding the clinical phenotype of autosomal dominant dyskeratosis congenita caused by TERT mutations. *Haematologica* **93**, 943–944 (2008).
274. Yao, L. *et al.* Spectrum and prevalence of FP/TMEM127 gene mutations in pheochromocytomas and paragangliomas. *JAMA* **304**, 2611–2619 (2010).
275. Toledo, S. P. A. *et al.* Penetrance and clinical features of pheochromocytoma in a six-generation family carrying a germline TMEM127 mutation. *J. Clin. Endocrinol. Metab.* **100**, E308-318 (2015).
276. Chompret, A. *et al.* P53 germline mutations in childhood cancers and cancer risk for carrier individuals. *Br. J. Cancer* **82**, 1932–1937 (2000).
277. 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).
278. Olivier, M. *et al.* Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype. *Cancer Res.* **63**, 6643–6650 (2003).
279. 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).
280. 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).
281. Northrup, H., Krueger, D. A., & International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 Iinternational Tuberous Sclerosis Complex Consensus Conference. *Pediatr. Neurol.* **49**, 243–254 (2013).
282. Krueger, D. A., Northrup, H., & International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr. Neurol.* **49**, 255–265 (2013).
283. Au, K. S. *et al.* Genotype/phenotype correlation in 325 individuals referred for a diagnosis of tuberous sclerosis complex in the United States. *Genet. Med. Off. J. Am. Coll. Med. Genet.* **9**, 88–100 (2007).
284. Frantzen, C., Klasson, T. D., Links, T. P. & Giles, R. H. Von Hippel-Lindau Syndrome. in *GeneReviews(®)* (eds. Pagon, R. A. et al.) (University of Washington, Seattle, 1993).
285. Mannelli, M. *et al.* Genetics and biology of pheochromocytoma. *Exp. Clin. Endocrinol. Diabetes Off. J. Ger. Soc. Endocrinol. Ger. Diabetes Assoc.* **115**, 160–165 (2007).
286. Lonser, R. R. *et al.* von Hippel-Lindau disease. *Lancet Lond. Engl.* **361**, 2059–2067 (2003).
287. Maher, E. R., Neumann, H. P. & Richard, S. von Hippel-Lindau disease: a clinical and scientific review. *Eur. J. Hum. Genet. EJHG* **19**, 617–623 (2011).
288. Auber, F. *et al.* Management of Wilms tumors in Drash and Frasier syndromes. *Pediatr. Blood Cancer* **52**, 55–59 (2009).
289. Dome, J. S. & Huff, V. Wilms Tumor Predisposition. in *GeneReviews(®)* (eds. Pagon, R. A. et al.) (University of Washington, Seattle, 1993).
290. Scott, R. H. *et al.* Surveillance for Wilms tumour in at-risk children: pragmatic recommendations for best practice. *Arch. Dis. Child.* **91**, 995–999 (2006).

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