OncoGeneDx: Hereditary Prostate Cancer Panel

PANEL GENE LIST

ATM, BRCA1, BRCA2, BRIP1, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, RAD51C, RAD51D, TP53*

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

CLINICAL FEATURES

In the general population, approximately 12.9% individuals will develop prostate cancer in their lifetime.[1] Most cases of prostate cancer develop sporadically. Between 4.6% and 11.8% of prostate cancer cases are thought to be due to a hereditary predisposition.[2,3] Factors that may be associated with hereditary prostate cancer include young age at diagnosis, multiple family members affected with prostate cancer and/or the association of prostate cancer with other cancers such as breast, ovarian, or pancreatic cancer.

Germline BRCA2 pathogenic variants account for the majority of inherited prostate cancer cases.[3] Pathogenic variants in ATM, BRCA1, BRIP1, CHEK2, HOXB13, NBN, PALB2, RAD51C, RAD51D, TP53 and the Lynch syndrome genes (MLH1, MSH2, MSH6, PMS2, and EPCAM) have also been linked to an increased risk of prostate cancer.[3–9] Most of the genes on this panel are associated with well-described cancer syndromes and have published consensus management guidelines; however, HOXB13 has only recently been described in association with an increased cancer risk. Since the cancer risk for this gene is not yet well defined, no consensus guidelines for medical management are available. The cancers that are associated with pathogenic variants in each of the genes are outlined in the attached table.

INHERITANCE PATTERN

All of the genes on this panel are associated with an autosomal dominant 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). 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. 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 16 genes included in the OncoGeneDx Hereditary Prostate 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 hereditary predisposition to prostate 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

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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 Association
ATM[10–15]	SERINE-PROTEIN KINASE ATM	AD	Breast, colon & pancreatic cancer
		AR	Ataxia telangiectasia
BRCA1[16–26]	BREAST CANCER TYPE 1 SUSCEPTIBILITY PROTEIN	AD	Hereditary Breast and Ovarian Cancer (HBOC) syndrome: breast, ovarian, pancreatic, prostate & endometrial serous cancer
BRCA2[16–23,25,26]	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[3,10,27,28]	FANCONI ANEMIA GROUP J PROTEIN	AD	Breast & ovarian cancer
		AR	Fanconi anemia
CHEK2[10,11,24,29–35]	SERINE/THREONINE-PROTEIN KINASE CHK2	AD	Breast, colon, prostate, gastric & thyroid cancer
EPCAM[36–41]	EPITHELIAL CELL ADHESION MOLECULE	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
HOXB13[42–44]	HOMEOBOX PROTEIN HOX-B13	AD	Prostate cancer

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MLH1[36,38–41,45,46]	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[36–41,45,46]	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[36,38–41,45,47]	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
NBN[48–54]	NIBRIN	AD	Breast & prostate cancer, non-Hodgkin lymphoma
		AR	Nijmegen breakage syndrome
PALB2[10,55–60]	PARTNER AND LOCALIZER OF BRCA2	AD	Breast, pancreatic, & ovarian cancer
		AR	Fanconi anemia
PMS2[36,38–41,61,62]	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
RAD51C[63–66]	DNA REPAIR PROTEIN RAD51 HOMOLOG 3	AD	Breast & ovarian cancer
		AR	Fanconi anemia
RAD51D[63,64,67,68]	DNA REPAIR PROTEIN RAD51 HOMOLOG 4	AD	Breast & ovarian cancer
TP53[24,69–73]	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.

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*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

REFERENCES:

1.Probability of Developing or Dying of Cancer - Surveillance Research Program. Available at: https://surveillance.cancer.gov/devcan/. (Accessed: 18th September 2017)
2.Carter, B. S., Beaty, T. H., Steinberg, G. D., Childs, B. & Walsh, P. C. Mendelian inheritance of familial prostate cancer. Proc. Natl. Acad. Sci. U. S. A. 89, 3367–3371 (1992).
3.Pritchard, C. C. et al. Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. N. Engl. J. Med. 375, 443–453 (2016).
4.Thompson, D., Easton, D. F. & Breast Cancer Linkage Consortium. Cancer Incidence in BRCA1 mutation carriers. J. Natl. Cancer Inst. 94,1358–1365 (2002).
5.Hwang, S.-J., Lozano, G., Amos, C. I. & Strong, L. C. Germline p53 mutations in a cohort with childhood sarcoma: sex differences in cancerrisk. Am. J. Hum. Genet. 72, 975–983 (2003).
6.Cybulski, C. et al. An inherited NBN mutation is associated with poor prognosis prostate cancer. Br. J. Cancer 108, 461–468 (2013).
7.Huang, H. & Cai, B. G84E mutation in HOXB13 is firmly associated with prostate cancer risk: a meta-analysis. Tumour Biol. J. Int. Soc. Oncodevelopmental Biol. Med. 35, 1177–1182 (2014).
8.Ryan, S., Jenkins, M. A. & Win, A. K. Risk of prostate cancer in Lynch syndrome: a systematic review and meta-analysis. CancerEpidemiol. Biomark. Prev. Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prev. Oncol. 23, 437–449 (2014).
9.Leongamornlert, D. et al. Frequent germline deleterious mutations in DNA repair genes in familial prostate cancer cases are associated with advanced disease. Br. J. Cancer 110, 1663–1672 (2014).
10.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).
11.Einarsdóttir, K. et al. Effect of ATM, CHEK2 and ERBB2 TAGSNPs and haplotypes on endometrial cancer risk. Hum. Mol. Genet. 16, 154–164 (2007).
12.Renwick, A. et al. ATM mutations that cause ataxia-telangiectasia are breast cancer susceptibility alleles. Nat. Genet. 38, 873–875 (2006).
13.Roberts, N. J. et al. ATM mutations in patients with hereditary pancreatic cancer. Cancer Discov. 2, 41–46 (2012).
14.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).
15.Thompson, D. et al. Cancer risks and mortality in heterozygous ATM mutation carriers. J. Natl. Cancer Inst. 97, 813–822 (2005).
16.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).
17.Antoniou, A. et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Seriesunselected for family history: a combined analysis of 22 studies. Am. J. Hum. Genet. 72, 1117–1130 (2003).
18.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).
19.Chen, S. & Parmigiani, G. Meta-analysis of BRCA1 and BRCA2 penetrance. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 25, 1329–1333(2007).
20.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).
21.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).
22.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).
23.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).
24.Pennington, K. P. et al. BRCA1, TP53, and CHEK2 germline mutations in uterine serous carcinoma. Cancer 119, 332–338 (2013).
25.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).
26.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).
27.Ramus, S. J. et al. Germline Mutations in the BRIP1, BARD1, PALB2, and NBN Genes in Women With Ovarian Cancer. J. Natl. CancerInst. 107, (2015).
28.Ghazwani, Y. et al. Clinical characteristics and genetic subtypes of Fanconi anemia in Saudi patients. Cancer Genet. 209, 171–176(2016).
29.Cybulski, C. et al. CHEK2 is a multiorgan cancer susceptibility gene. Am. J. Hum. Genet. 75, 1131–1135 (2004).
30.Dong, X. et al. Mutations in CHEK2 associated with prostate cancer risk. Am. J. Hum. Genet. 72, 270–280 (2003).
31.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).
32.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).
33.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).
34.Seppälä, E. H. et al. CHEK2 variants associate with hereditary prostate cancer. Br. J. Cancer 89, 1966–1970 (2003).
35.Suchy, J. et al. CHEK2 mutations and HNPCC-related colorectal cancer. Int. J. Cancer 126, 3005–3009 (2010).
36. 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).
37.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 uniquegenotype and immunophenotype. J. Clin. Pathol. 66, 631–633 (2013).

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38.Vasen, H. F. et al. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. Gastroenterology110, 1020–1027 (1996).
39. Win, A. K. et al. Colorectal and other cancer risks for carriers and noncarriers from families with a DNA mismatch repair gene mutation: aprospective cohort study. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 30, 958–964 (2012).
40.Durno, C. A., Holter, S., Sherman, P. M. & Gallinger, S. The gastrointestinal phenotype of germline biallelic mismatch repair genemutations. Am. J. Gastroenterol. 105, 2449–2456 (2010).
41. Wimmer, K. & Kratz, C. P. Constitutional mismatch repair-deficiency syndrome. Haematologica 95, 699–701 (2010).
42.Ewing, C. M. et al. Germline mutations in HOXB13 and prostate-cancer risk. N. Engl. J. Med. 366, 141–149 (2012).
43.Akbari, M. R. et al. Association between germline HOXB13 G84E mutation and risk of prostate cancer. J. Natl. Cancer Inst. 104, 1260–1262 (2012).
44.Alanee, S., Couch, F. & Offit, K. Association of a HOXB13 variant with breast cancer. N. Engl. J. Med. 367, 480–481 (2012).
45.Bonadona, V. et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA 305,2304–2310 (2011).
46.Quehenberger, F., Vasen, H. F. A. & van Houwelingen, H. C. Risk of colorectal and endometrial cancer for carriers of mutations of thehMLH1 and hMSH2 gene: correction for ascertainment. J. Med. Genet. 42, 491–496 (2005).
47.Baglietto, L. et al. Risks of Lynch syndrome cancers for MSH6 mutation carriers. J. Natl. Cancer Inst. 102, 193–201 (2010).
48.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).
49.Steffen, J. et al. Increased cancer risk of heterozygotes with NBS1 germline mutations in Poland. Int. J. Cancer 111, 67–71 (2004).
50.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).
51.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 60publications with 111 individual studies. Mutagenesis 28, 683–697 (2013).
52.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).
53.di Masi, A. & Antoccia, A. NBS1 Heterozygosity and Cancer Risk. Curr. Genomics 9, 275–281 (2008).
54.He, Y.-Z. et al. NBS1 Glu185Gln polymorphism and cancer risk: update on current evidence. Tumour Biol. J. Int. Soc. OncodevelopmentalBiol. Med. 35, 675–687 (2014).
55.Rahman, N. et al. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. Nat. Genet. 39, 165–167(2007).
56.Erkko, H. et al. A recurrent mutation in PALB2 in Finnish cancer families. Nature 446, 316–319 (2007).
57.Antoniou, A. C. et al. Breast-cancer risk in families with mutations in PALB2. N. Engl. J. Med. 371, 497–506 (2014).
58.Casadei, S. et al. Contribution of inherited mutations in the BRCA2-interacting protein PALB2 to familial breast cancer. Cancer Res. 71,2222–2229 (2011).
59.Jones, S. et al. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. Science 324, 217 (2009).
60.Slater, E. P. et al. PALB2 mutations in European familial pancreatic cancer families. Clin. Genet. 78, 490–494 (2010).
61.Senter, L. et al. The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. Gastroenterology 135, 419–428 (2008).
62.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).
63.Norquist, B. M. et al. Inherited Mutations in Women With Ovarian Carcinoma. JAMA Oncol. 2, 482–490 (2016).
64.Lilyquist, J. et al. Frequency of mutations in a large series of clinically ascertained ovarian cancer cases tested on multi-gene panelscompared to reference controls. Gynecol. Oncol. 147, 375–380 (2017).
65.Couch, F. J. et al. Associations Between Cancer Predisposition Testing Panel Genes and Breast Cancer. JAMA Oncol. 3, 1190–1196(2017).
66.Rashid, M. U., Muhammad, N., Faisal, S., Amin, A. & Hamann, U. Deleterious RAD51C germline mutations rarely predispose to breastand ovarian cancer in Pakistan. Breast Cancer Res. Treat. 145, 775–784 (2014).
67.Loveday, C. et al. Germline mutations in RAD51D confer susceptibility to ovarian cancer. Nat. Genet. 43, 879–882 (2011).
68.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).
69.Chompret, A. et al. P53 germline mutations in childhood cancers and cancer risk for carrier individuals. Br. J. Cancer 82, 1932–1937(2000).
70.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).
71.Olivier, M. et al. Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype. Cancer Res.63, 6643–6650 (2003).
72.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).
73.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).

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