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-CNVI). 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

207 Perry Parkway, Gaithersburg, MD 20877 | P: 301-519-2100 | F: 201-421-2010 | E: genedx@genedx.com

www.genedx.com
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 regions with inadequate sequence or copy number data by next generation sequencing (NGS). Reported clinically significant variants are confirmed by an appropriate method. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. 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 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.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Inheritance</th>
<th>Disease Associations</th>
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<tbody>
<tr>
<td>ATM&lt;sup&gt;10–15&lt;/sup&gt;</td>
<td>SERINE-PROTEIN KINASE ATM</td>
<td>AD</td>
<td>Breast, colon &amp; pancreatic cancer</td>
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<td></td>
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<td>AR</td>
<td>Ataxia telangiectasia</td>
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<td>BRCA&lt;sup&gt;16–26&lt;/sup&gt;</td>
<td>BREAST CANCER TYPE 1 SUSCEPTIBILITY PROTEIN</td>
<td>AD</td>
<td>Hereditary Breast and Ovarian Cancer (HBOC) syndrome: breast, ovarian, pancreatic, prostate &amp; endometrial serous cancer</td>
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<td>BRCA&lt;sup&gt;26–23,25,26&lt;/sup&gt;</td>
<td>BREAST CANCER TYPE 2 SUSCEPTIBILITY PROTEIN</td>
<td>AD</td>
<td>Hereditary Breast and Ovarian Cancer (HBOC) syndrome: breast, ovarian, pancreatic, prostate, melanoma &amp; endometrial serous cancer</td>
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<td>BRIPT&lt;sup&gt;1,10,27,28&lt;/sup&gt;</td>
<td>FANCONI ANEMIA GROUP J PROTEIN</td>
<td>AD</td>
<td>Breast &amp; ovarian cancer</td>
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<td>AR</td>
<td>Fanconi anemia</td>
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<tr>
<td>CHEK2&lt;sup&gt;10,11,24,29–35&lt;/sup&gt;</td>
<td>SERINE/THREONINE-PROTEIN KINASE CHK2</td>
<td>AD</td>
<td>Breast, colon, prostate, gastric &amp; thyroid cancer</td>
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<tr>
<td>EPCAM&lt;sup&gt;36–41&lt;/sup&gt;</td>
<td>EPITHELIAL CELL ADHESION MOLECULE</td>
<td>AD</td>
<td>Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate &amp; brain cancer, sebaceous neoplasms</td>
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<td></td>
<td></td>
<td>AR</td>
<td>Constitutional mismatch repair deficiency syndrome</td>
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<tr>
<td>HOXB13&lt;sup&gt;2–44&lt;/sup&gt;</td>
<td>HOMEBOX PROTEIN HOX-B13</td>
<td>AD</td>
<td>Prostate cancer</td>
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<tr>
<td>MLH&lt;sup&gt;136,38&lt;/sup&gt;</td>
<td>DNA MISMATCH REPAIR PROTEIN MLH1</td>
<td>AD</td>
<td>Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate &amp; brain cancer, sebaceous neoplasms</td>
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<td>AR</td>
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<tr>
<td>MSH2&lt;sup&gt;26–41,45,46&lt;/sup&gt;</td>
<td>DNA MISMATCH REPAIR PROTEIN MSH2</td>
<td>AD</td>
<td>Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate &amp; brain cancer, sebaceous neoplasms</td>
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<td>AR</td>
<td>Constitutional mismatch repair</td>
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<tr>
<td>Gene</td>
<td>Description</td>
<td>Inheritance Pattern</td>
<td>Phenotype</td>
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<td><strong>MSH6</strong>&lt;sup&gt;36,38&lt;/sup&gt;&lt;br&gt;-41,45,47</td>
<td>DNA MISMATCH REPAIR PROTEIN MSH6</td>
<td>AD</td>
<td>Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate &amp; brain cancer, sebaceous neoplasms</td>
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<td>AR</td>
<td>Constitutional mismatch repair deficiency syndrome</td>
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<tr>
<td><strong>NBN</strong>&lt;sup&gt;48–54&lt;/sup&gt;</td>
<td>NIBRIN</td>
<td>AD</td>
<td>Breast &amp; prostate cancer, non-Hodgkin lymphoma</td>
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<td>AR</td>
<td>Nijmegen breakage syndrome</td>
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<td><strong>PALB2</strong>&lt;sup&gt;10,5&lt;/sup&gt;&lt;br&gt;5–60</td>
<td>PARTNER AND LOCALIZER OF BRCA2</td>
<td>AD</td>
<td>Breast, pancreatic, &amp; ovarian cancer</td>
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<td></td>
<td></td>
<td>AR</td>
<td>Fanconi anemia</td>
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<tr>
<td><strong>PMS2</strong>&lt;sup&gt;36,38&lt;/sup&gt;&lt;br&gt;-41,61,62</td>
<td>MISMATCH REPAIR ENDONUCLEASE PMS2</td>
<td>AD</td>
<td>Lynch syndrome (LS): colorectal, endometrial, ovarian, gastric, pancreatic, biliary tract, urinary tract, small bowel, prostate &amp; brain cancer, sebaceous neoplasms</td>
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<td>AR</td>
<td>Constitutional mismatch repair deficiency syndrome</td>
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<td><strong>RAD51C</strong>&lt;sup&gt;6&lt;/sup&gt;&lt;br&gt;3–66</td>
<td>DNA REPAIR PROTEIN RAD51 HOMOLOG 3</td>
<td>AD</td>
<td>Breast &amp; ovarian cancer</td>
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<td><strong>RAD51D</strong>&lt;sup&gt;6&lt;/sup&gt;&lt;br&gt;3,64,67,68</td>
<td>DNA REPAIR PROTEIN RAD51 HOMOLOG 4</td>
<td>AD</td>
<td>Breast &amp; ovarian cancer</td>
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<tr>
<td><strong>TP53</strong>&lt;sup&gt;24,69–73&lt;/sup&gt;</td>
<td>CELLULAR TUMOR ANTIGEN P53</td>
<td>AD</td>
<td>Li-Fraumeni syndrome (LFS): breast cancer, sarcoma, brain cancer, hematologic malignancies, adrenocortical carcinoma, among others**</td>
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</table>

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

**References:**
1. Probability of Developing or Dying of Cancer - Surveillance Research Program. Available at: https://surveillance.cancer.gov/devcan/.
   (Accessed: 18th September 2017)
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).