Hereditary Endocrine Cancer Panel

Test code: ON0701

The Blueprint Genetics Hereditary Endocrine Cancer Panel analyzes 22 genes associated with inherited susceptibility to endocrine cancer.

Syndromes that contribute to increased risk of developing tumors of the endocrine system have predominantly autosomal dominant inheritance pattern. Pathogenic mutations are found in between 15 and 95% of the individual endocrine tumor syndromes. The Hereditary Endocrine Cancer Panel is suited for detecting heritable germline mutations and may not be used for the detection of somatic mutations in tumor tissue. This comprehensive Panel includes Hereditary Thyroid Cancer and Hereditary Paraganglioma-Pheochromocytoma Panels. All genes in this Panel are included in the Comprehensive Hereditary Cancer Panel.

About Hereditary Endocrine Cancer

Hereditary endocrine tumor syndromes result in overproduction of hormones, cause growth of tumors in endocrine glands and increase the lifetime risk of developing metastatic diseases, such as gastrointestinal and pancreatic carcinomas. Genetic conditions that cause tumors of the endocrine glands include rare inherited syndromes such as multiple endocrine neoplasias (MEN1, RET, CDKN1B), familial medullary thyroid carcinoma (RET), familial isolated pituitary adenoma (AIP), Carney complex (PRKAR1A), Hirschsprung disease (RET), and Von Hippel-Lindau disease (VHL). Syndromes associated specifically with hereditary thyroid cancer and hereditary paraganglioma-pheochromocytoma are described in the subpanels for these conditions. Prevalences of individual hereditary endocrine tumor syndromes varies from very rare to 7:100 000.

Availability

Results in 3-4 weeks. We do not offer a maternal cell contamination (MCC) test at the moment. We offer prenatal testing only for cases where the maternal cell contamination studies (MCC) are done by a local genetic laboratory. Read more: http://blueprintgenetics.com/faqs/#prenatal

Gene set description

Genes in the Hereditary Endocrine Cancer Panel and their clinical significance

<table>
<thead>
<tr>
<th>Gene</th>
<th>Associated phenotypes</th>
<th>Inheritance</th>
<th>ClinVar</th>
<th>HGMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIP</td>
<td>Pituitary adenoma, familial isolated</td>
<td>AD</td>
<td>54</td>
<td>106</td>
</tr>
<tr>
<td>APC</td>
<td>Gardner syndrome, Desmoid disease, hereditary, Familial adenomatous polyposis</td>
<td>AD</td>
<td>294</td>
<td>1780</td>
</tr>
<tr>
<td>CDC73</td>
<td>Carcinoma, parathyroid, Hyperparathyroidism, Hyperparathyroidism-jaw tumor syndrome</td>
<td>AD</td>
<td>23</td>
<td>86</td>
</tr>
<tr>
<td>CDKN1B</td>
<td>Multiple endocrine neoplasia</td>
<td>AD</td>
<td>9</td>
<td>23</td>
</tr>
<tr>
<td>DICER*</td>
<td>DICER1 syndrome</td>
<td>AD</td>
<td>96</td>
<td>109</td>
</tr>
<tr>
<td>FH</td>
<td>Hereditary leiomyomatosis and renal cell cancer</td>
<td>AD/AR</td>
<td>89</td>
<td>161</td>
</tr>
<tr>
<td>MAX</td>
<td>Pheochromocytoma</td>
<td>AD</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>MEN1</td>
<td>Hyperparathyroidism, familial primary, Multiple endocrine neoplasia</td>
<td>AD</td>
<td>124</td>
<td>699</td>
</tr>
<tr>
<td>MET</td>
<td>Deafness, Renal cell carcinoma, papillary</td>
<td>AD/AR</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>NF1*</td>
<td>Watson syndrome, Neurofibromatosis, Neurofibromatosis-Noonan syndrome</td>
<td>AD</td>
<td>261</td>
<td>2607</td>
</tr>
</tbody>
</table>

https://blueprintgenetics.com/
<table>
<thead>
<tr>
<th>Gene</th>
<th>Genomic location HG19</th>
<th>HGVS</th>
<th>RefSeq</th>
<th>RS-number</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIP</td>
<td>Chr11:67250410</td>
<td>c.-220G&gt;A</td>
<td>NM_003977.2</td>
<td>rs267606540</td>
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<tr>
<td>AIP</td>
<td>Chr11:67250359</td>
<td>c.-270_269delinsAA</td>
<td>NM_003977.2</td>
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<tr>
<td>APC</td>
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<td>c.-125delA</td>
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<td>Chr5:112043225</td>
<td>c.-190G&gt;A</td>
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<td>c.-191T&gt;C</td>
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<td>c.-192A&gt;G/T</td>
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<td>CDKN1B</td>
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<td>c.-29_-26delAGAG</td>
<td>NM_004064.3</td>
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</tr>
</tbody>
</table>

*Some regions of the gene are duplicated in the genome leading to limited sensitivity within the regions. Thus, low-quality variants are filtered out from the duplicated regions and only high-quality variants confirmed by other methods are reported out. Read more.*

Gene, refers to HGNC approved gene symbol; Inheritance to inheritance patterns such as autosomal dominant (AD), autosomal recessive (AR) and X-linked (XL); ClinVar, refers to a number of variants in the gene classified as pathogenic or likely pathogenic in ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/); HGMD, refers to a number of variants with possible disease association in the gene listed in Human Gene Mutation Database (HGMD, http://www.hgmd.cf.ac.uk/ac/). The list of associated (gene specific) phenotypes are generated from CDG (http://research.nhgri.nih.gov/CGD/) or Orphanet (http://www.orpha.net/) databases.

Non-coding disease causing variants covered by the panel

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CDKN1B Chr12:12870741 c.-29_-26delAGAG NM_004064.3 rs869312166
CDKN1B Chr12:12870317 c.-454_-451delTTCC NM_004064.3 rs756201010
CDKN1B Chr12:12870694 c.-80C>T NM_004064.3 rs551236750
NF1 Chr17:29577934 c.4110+1802delA NM_001042492.2 rs863224944
NF1 Chr17:29657848 c.5812+332A>G NM_001042492.2 rs863224491
PRKAR1A Chr17:66508690 c.-71G>A NM_002734.4
PTEN Chr10:89623462 c.-765G>A NM_000314.4
PTEN Chr10:89623365 c.-862G>T NM_000314.4 rs587776675
TMEM127 Chr2:96931137 c.-18G>T NM_017849.3 rs121908813
VHL Chr3:10183453 c.-75_-55delCGACCGAGCTCCGCCCCGCG NM_000551.3 rs727503744
WRN Chr8:30966107 c.2089-3024A>G NM_000553.4 rs281865157

Test performance

Blueprint Genetics offers a comprehensive Hereditary Endocrine Cancer Panel that covers classical genes associated with Birt-Hogg-Dube syndrome, carney complex, Carney-Stratakis syndrome, Cowden syndrome, DICER1 syndrome, endocrine cancer, familial adenomatous polyposis, familial isolated hyperparathyroidism, familial isolated pituitary adenoma, familial medullary thyroid carcinoma, familial multinoval goiter, familial parathyroid adenoma, hereditary parangangioma-pheochromocytoma syndromes, Hirschsprung disease (HSCR), hyperparathyroidism-jaw tumor syndrome, Li-Fraumeni syndrome 1, multiple endocrine neoplasia, neurofibromatosis type 1, primary pigmented nodular adrenocortical disease, Von Hippel-Lindau disease and Werner syndrome. The genes are carefully selected based on the existing scientific evidence, our experience and most current mutation databases. Candidate genes are excluded from this first-line diagnostic test. The test does not recognise balanced translocations or complex inversions, and it may not detect low-level mosaicism. The test should not be used for analysis of sequence repeats or for diagnosis of disorders caused by mutations in the mitochondrial DNA.

Analytical validation is a continuous process at Blueprint Genetics. Our mission is to improve the quality of the sequencing process and each modification is followed by our standardized validation process. Average sensitivity and specificity in Blueprint NGS Panels is 99.3% and 99.9% for detecting SNPs. Sensitivity to for indels vary depending on the size of the alteration: 1-10bps (96.0%), 11-20 bps (88.4%) and 21-30 bps (66.7%). The longest detected indel was 46 bps by sequence analysis. Detection limit for Del/Dup (CNV) analysis varies through the genome depending on exon size, sequencing coverage and sequence content. The sensitivity is 71.5% for single exon deletions and duplications and 99% for three exons' deletions and duplications. We have validated the assays for different starting materials including EDTA-blood, isolated DNA (no FFPE) and saliva that all provide high-quality results. The diagnostic yield varies substantially depending on the used assay, referring healthcare professional, hospital and country. Blueprint Genetics' Plus Analysis (Seq+Del/Dup) maximizes the chance to find molecular genetic diagnosis for your patient although Sequence Analysis or Del/Dup Analysis may be cost-effective first line test if your patient's phenotype is suggestive for a specific mutation profile.

Bioinformatics

The sequencing data generated in our laboratory is analyzed with our proprietary data analysis and annotation pipeline, integrating state-of-the-art algorithms and industry-standard software solutions. Incorporation of rigorous quality control steps throughout the workflow of the pipeline ensures the consistency, validity and accuracy of results. The highest relevance in the reported variants is achieved through elimination of false positive findings based on variability data for thousands of publicly available human reference sequences and validation against our in-house curated mutation database as well as the most current and relevant human mutation databases. Reference databases currently used are the 1000 Genomes Project (http://www.1000genomes.org), the NHLBI GO Exome Sequencing Project (ESP; http://evs.gs.washington.edu/EVS), the Exome Aggregation Consortium (ExAC; http://exac.broadinstitute.org), ClinVar database of genotype-phenotype associations (http://www.ncbi.nlm.nih.gov/clinvar) and the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk). The consequence of variants in coding and splice regions are estimated using the following in silico variant prediction tools: SIFT (http://sift.jcvi.org), Polyphen (http://genetics.bwh.harvard.edu/pph2/), and Mutation Taster (http://www.mutationtaster.org).

https://blueprintgenetics.com/
Through our online ordering and statement reporting system, Nucleus, the customer can access specific details of the analysis of the patient. This includes coverage and quality specifications and other relevant information on the analysis. This represents our mission to build fully transparent diagnostics where the customer gains easy access to crucial details of the analysis process.

**Clinical interpretation**

In addition to our cutting-edge patented sequencing technology and proprietary bioinformatics pipeline, we also provide the customers with the best-informed clinical report on the market. Clinical interpretation requires fundamental clinical and genetic understanding. At Blueprint Genetics our geneticists and clinicians, who together evaluate the results from the sequence analysis pipeline in the context of phenotype information provided in the requisition form, prepare the clinical statement. Our goal is to provide clinically meaningful statements that are understandable for all medical professionals, even without training in genetics.

Variants reported in the statement are always classified using the Blueprint Genetics Variant Classification Scheme modified from the ACMG guidelines (Richards et al. 2015), which has been developed by evaluating existing literature, databases and with thousands of clinical cases analyzed in our laboratory. Variant classification forms the cornerstone of clinical interpretation and following patient management decisions. Our statement also includes allele frequencies in reference populations and in silico predictions. We also provide PubMed IDs to the articles or submission numbers to public databases that have been used in the interpretation of the detected variants. In our conclusion, we summarize all the existing information and provide our rationale for the classification of the variant.

A final component of the analysis is the Sanger confirmation of the variants classified as likely pathogenic or pathogenic. This does not only bring confidence to the results obtained by our NGS solution but establishes the mutation specific test for family members. Sanger sequencing is also used occasionally with other variants reported in the statement. In the case of variant of uncertain significance (VUS) we do not recommend risk stratification based on the genetic finding. Furthermore, in the case VUS we do not recommend use of genetic information in patient management or genetic counseling. For some cases Blueprint Genetics offers a special free of charge service to investigate the role of identified VUS.

We constantly follow genetic literature adapting new relevant information and findings to our diagnostics. Relevant novel discoveries can be rapidly translated and adopted into our diagnostics without delay. These processes ensure that our diagnostic panels and clinical statements remain the most up-to-date on the market.

**CPT codes**

SEQ 81437
DEL/DUP 81438

**Accepted sample types**

- EDTA blood, min. 1 ml
- Purified DNA, min. 5μg
- Saliva (Oragene DNA OG-500 kit)

Label the sample tube with your patient’s name, date of birth and the date of sample collection.

Note that we do not accept DNA samples isolated from formalin-fixed paraffin-embedded (FFPE) tissue.

**Resources**

- BHD Foundation
- Cancer.Net - Cowden Syndrome
- Cancer.Net - Cowden Syndrome
- Familial Isolated Pituitary Adenoma
- Cancer.Net - Attenuated Familial Adenomatous Polyposis
- HypoPARAthyroidism
- International Osteoporosis Foundation - Hyperparathyroidism
- Thyroid Cancer Canada
- Parathyroid.com
- Adrenaltumors.org
- Short Bowel Syndrome Foundation
- International Foundation for Functional Gastrointestinal Disorders
- Li-Fraumeni Syndrome Association
- American Multiple Endocrine Neoplasia Support
- VHL Alliance
- International Registry of Werner Syndrome
- NORD - Birt-Hogg-Dubé Syndrome
- NORD - Carney Complex
- NORD - Familial Adenomatous Polyposis
- NORD - Thyroid Cancer
- NORD - Pheochromocytoma
- NORD - Hirschsprung Disease
- NORD - Multiple Endocrine Neoplasia Type 1
- NORD - Multiple Endocrine Neoplasia Type 2
- NORD - Neurofibromatosis Type 1 (NF1)
- NORD - Von Hippel-Lindau Syndrome
- NORD - Werner Syndrome
- Gene Reviews - Birt-Hogg-Dube Syndrome
- Gene Reviews - Carney Complex
- Gene Reviews - DICER1-Related Disorders
- Gene Reviews - CDC73-Related Disorders
- Gene Reviews - APC-Associated Polyposis Conditions
- Gene Reviews - Multiple Endocrine Neoplasia Type 1
- Gene Reviews - Multiple Endocrine Neoplasia Type 2
- Gene Reviews - Von Hippel-Lindau Syndrome
- Gene Reviews - DICER1-Related Disorders
- Gene Reviews - Hereditary Paraganglioma-Pheochromocytoma Syndromes
- Gene Reviews - Hirschsprung Disease
- Gene Reviews - Li-Fraumeni Syndrome
- Gene Reviews - Multiple Endocrine Neoplasia Type 1
- Gene Reviews - Multiple Endocrine Neoplasia Type 2
- Gene Reviews - Neurofibromatosis 1
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- Gene Reviews - Werner Syndrome

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