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.

ICD & CPT codes

CPT codes

SEQ 81437  DEL/DUP 81438

Sample requirements

- 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
HypoPARAthroidism
International Osteoporosis Foundation - Hyperparathyroidism
Tyroid Cancer Canada
Parathyroid.com
Adrenaltumors.org
Short Bowel Syndrome Foundation

https://blueprintgenetics.com
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 multinodular goiter, familial parathyroid adenoma, hereditary paraganglioma-pheochromocytoma syndromes, Hirschsprung disease (HSCR), hyperparathyroidism-jaw tumor syndrome, Li-Fraumeni syndrome, 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 recognize 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: 1-10 bps (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).

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 corner stone 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.

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