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*, ETBV6, FANCC, FANCN, 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, RECLQ, RET*, RUNX1, SAMD9, SAMD9L, SCG5/GREM1*, SDHA*, SDHA, 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. 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 RECLQ. 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.
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
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.

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Test Information Sheet


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