OncoGeneDx: Renal Cancer Panel

Panel Gene List: *BAP1, EPCAM*, FH, FLCN, MET, MITF, MLH1, MSH2, MSH6, PMS2, PTEN, SDHB, SDHC, SDHD, TP53, TSC1, TSC2, VHL*

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

Clinical Features:

In the general population, approximately 1.6% of individuals will develop renal cancer in their lifetime.[1] Most cases of renal cancers develop sporadically. It has been estimated that approximately 3-5% of renal cancer cases are due to a hereditary predisposition.[2,3] The features of a personal and/or family history of cancer that are suggestive of a hereditary cancer predisposition include: young ages at diagnosis, multiple primary cancers in a single individual, diagnosis of a cancer type that is not common in general population (such as renal cancer), and several relatives affected with cancer spanning multiple generations.

Hereditary renal cancer has long been described in association with several phenotypically distinct syndromes. These include von Hippel-Lindau disease (*VHL*), hereditary papillary renal cancer (*MET*), Birt-Hogg-Dubé syndrome (*FLCN*), hereditary leiomyomatosis and renal cell carcinoma (*FH*) and tuberous sclerosis complex (*TSC1, TSC2*). Pathogenic variants in these six aforementioned genes account for a significant portion of hereditary renal cancer and have been well described in the literature. In addition, several other well described syndromes include a risk of renal cancer as a minor feature. These include Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*), Cowden syndrome (*PTEN*), Li-Fraumeni syndrome (*TP53*) and hereditary paraganglioma/pheochromocytoma syndrome (*SDHB, SDHC, SDHD*). Management guidelines are available for these genes.

Pathogenic variants in newer genes, such as *BAP1* and *MITF,* have been identified in families with renal cancer and may increase the risk for other cancers as well. The evidence available to date may be derived from a small number of patients with wide confidence intervals or is based upon an ethnic cohort with one specific variant. Accurate risk assessment may be complicated by the low penetrance of pathogenic variants in these genes and/or ascertainment bias. Since the cancer risks are not yet well defined, no consensus guidelines for medical management are available for these genes.

Inheritance Pattern:

All 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. 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 is 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 *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 NGS. Reported clinically significant variants are confirmed by an appropriate method. Sequence variants are reported according to the Human Genome Variation Society (HGVS) guidelines. Copy number variants are reported based on the probe coordinates, the coordinates of the exons involved, or precise breakpoints when known. 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 18 genes included in the OncoGeneDx Renal 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.

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 Associations
BAP1[4,5]	UBIQUITIN CARBOXYL-TERMINAL HYDROLASE BAP1	AD	Uveal/cutaneous melanoma, mesothelioma & renal cancer
EPCAM[6–11]	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
FH[12–16]	FUMARATE HYDRATASE, MITOCHONDRIAL	AD	Hereditary leiomyomatosis and renal cell cancer (HLRCC): Renal cancer (type II papillary), leiomyomas, pheochromocytoma, paraganglioma
		AR	Fumarate hydratase deficiency
FLCN[17–21]	FOLLICULIN	AD	Birt-Hogg-Dubé syndrome (BHD): Renal cancer
MET[22–25]	HEPATOCYTE GROWTH FACTOR RECEPTOR	AD	Hereditary papillary renal carcinoma (HPRC): Renal cancer (type I papillary)
MITF[26–28]	MICROPHTHALMIA-ASSOCIATED TRANSCRIPTION FACTOR	AD	Renal cancer & melanoma
MLH1[6,8–11,29,30]	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[6–11,29,30]	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[6,8–11,29,30]	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
PMS2[6,8–11,31,32]	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
PTEN[29,33–36]	PHOSPHATIDYLINOSITOL 3,4,5-TRISPHOSPHATE 3-PHOSPHATASE AND DUAL-SPECIFICITY PROTEIN PHOSPHATASE PTEN	AD	*PTEN* hamartoma tumor syndrome (PHTS): Breast, thyroid, endometrial, colon, melanoma & renal cancer, gastrointestinal polyps, Lhermitte-Duclos disease
SDHB[37–40]	SUCCINATE DEHYDROGENASE [UBIQUINONE] IRON-SULFUR SUBUNIT, MITOCHONDRIAL	AD	Hereditary paraganglioma/ pheochromocytoma (PGL/PCC) syndrome: Paraganglioma, pheochromocytoma, renal cancer, GIST

		AR	Isolated complex II deficiency
SDHC[37,38,41–43]	SUCCINATE DEHYDROGENASE CYTOCHROME B560 SUBUNIT, MITOCHONDRIAL	AD	Hereditary paraganglioma/ pheochromocytoma (PGL/PCC) syndrome: Paraganglioma, pheochromocytoma, renal cancer, GIST
SDHD[37–39,44,45]	SUCCINATE DEHYDROGENASE [UBIQUINONE] CYTOCHROME B SMALL SUBUNIT, MITOCHONDRIAL	AD	Hereditary paraganglioma/ pheochromocytoma (PGL/PCC) syndrome: Paraganglioma, pheochromocytoma, renal cancer, GIST, thyroid cancer
		AR	Isolated complex II deficiency
TP53[46–51]	CELLULAR TUMOR ANTIGEN P53	AD	Li-Fraumeni syndrome (LFS): Breast cancer, sarcoma, brain cancer, hematologic malignancies, adrenocortical carcinoma, among others**
TSC1[52–54]	HAMARTIN	AD	Tuberous sclerosis complex (TSC): Renal cancer/tumors, CNS tumors (subependymal nodules and subependymal giant cell astrocytomas), hamartomatous tumors (cardiac rhabdomyomas and angiomyolipomas)
TSC2[52–54]	TUBERIN	AD	Tuberous sclerosis complex (TSC): Renal cancer/tumors, CNS tumors (subependymal nodules and subependymal giant cell astrocytomas), hamartomatous tumors (cardiac rhabdomyomas and angiomyolipomas)
VHL[55–58]	VON HIPPEL-LINDAU DISEASE TUMOR SUPPRESSOR	AD	von Hippel-Lindau (VHL) disease: Renal cancer (clear cell), pancreatic neuroendocrine tumors, hemangioblastoma, pheochromocytoma, endolymphatic sac tumors

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
GIST – Gastrointestinal stromal tumor
MLPA – Multiplex ligation-dependent probe amplification

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