OncoGeneDx: Hereditary MDS/Leukemia Panel

Panel Gene List: *ANKRD26, CEBPA*, DDX41, ETV6, GATA2, RUNX1, SAMD9, SAMD9L, SRP72, TERC, TERT, TP53*
*Testing includes sequencing and deletion/duplication analysis for all genes except *CEBPA* (seq only).

Clinical Features:
In the general population, approximately 1.5% of individuals will develop leukemia in their lifetime.[1] Most hematological malignancies develop sporadically; however, approximately 11% to 18% of hematological cancer cases are thought to be due to a hereditary predisposition.[2–4] Features suggestive of hereditary hematological cancer predisposition may include early age of diagnosis of leukemia or myelodysplastic syndrome (MDS), multiple family members affected with thrombocytopenia, aplastic anemia, hematological cancer, or MDS, and in some cases, the presence of certain solid tumors or other health problems in the family.

The OncoGeneDx Hereditary MDS/Leukemia Panel includes analysis of 12 cancer predisposition genes that have been implicated in hematological malignancy predisposition. This panel includes *TP53*, which is associated with Li-Fraumeni syndrome, a hereditary cancer predisposition syndrome with consensus management guidelines. Additionally, pathogenic variants in *TERC* and *TERT* (dyskeratosis congenita/telomere disorder), *SAMD9*, and *SAMD9L* have published expert opinion management guidelines available.[5,6] Pathogenic variants in *ANKRD26, CEBPA, DDX41, ETV6, GATA2, RUNX1,* and *SRP72* have also been reported in association with hereditary hematological malignancy. Since the cancer risks for these seven genes are not yet well defined, no consensus medical management guidelines have been published. However, surveillance and management recommendations for individuals with genetic predisposition to hematologic malignancies are available.[7] The cancers that are associated with pathogenic variants in each of the genes are outlined in the table below.

Inheritance Pattern:
All of the genes on this panel are associated with autosomal dominant cancer risk. Additionally, inheritance of biallelic pathogenic variants in *SAMD9* are associated with normophosphatemic familial tumoral calcinosis while biallelic pathogenic variants in *TERT* are associated with a severe autosomal recessive form of dyskeratosis congenita. The specifics of this inheritance are outlined in the table below.

Specimen Requirements:
Cultured skin fibroblasts are the preferred specimen type for germline genetic testing in individuals who may have acquired somatic mutations in their peripheral blood lymphocytes

(active leukemias, chronic leukemias, myeloproliferative disorders, active forms of some lymphomas).

Blood and buccal specimens are generally acceptable for individuals with active or past histories of a hematologic disease type that does not typically infiltrate the peripheral blood (Hodgkin lymphoma, follicular lymphoma, diffuse large B-cell lymphoma, multiple myeloma, others).

Please visit the specimen requirements section of the GeneDx website for additional information on sample types.

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). 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. For *CEBPA*, only 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.

Test Sensitivity:
The clinical sensitivity of sequencing and deletion/duplication analysis of the 12 genes included in the OncoGeneDx Hereditary MDS/Leukemia 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, a genetic rescue event (i.e. loss of heterozygosity, somatic reversion, uniparental disomy, etc), 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
ANKRD26[8–11]	ANKYRIN REPEAT DOMAIN-CONTAINING PROTEIN 26	AD	Thrombocytopenia-2: Myeloid malignancies (AML, MDS, CML)
CEBPA[12,13]	CCAAT/ENHANCER-BINDING PROTEIN, ALPHA	AD	CEBPA-associated familial acute myeloid leukemia: AML
DDX41[14–16]	DEAD/H BOX 41	AD	AML, MDS
ETV6[17,18]	ETS VARIANT GENE 6	AD	Thrombocytopenia-5: MDS, AML, ALL
GATA2[19–23]	GATA-BINDING PROTEIN 2	AD	Familial MDS/AML, monocytopenia and mycobacterial infection (MonoMAC) syndrome, Emberger syndrome
RUNX1[24–27]	RUNT-RELATED TRANSCRIPTION FACTOR 1	AD	Familial platelet disorder with propensity to acute myeloid leukemia (FPD/AML), MDS
SAMD9[6,28–32]	STERILE ALPHA MOTIF DOMAIN-CONTAINING PROTEIN 9	AD	AML, MDS; Myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy (MIRAGE) syndrome
		AR	Normophosphatemic familial

Gene	Protein	Inheritance	Disease Associations
			tumoral calcinosis (NFTC)
SAMD9L[6,32–34]	STERILE ALPHA MOTIF DOMAIN-CONTAINING PROTEIN 9-LIKE	AD	AML, MDS, Ataxia–pancytopenia syndrome (ATXPC)
SRP72[35]	SIGNAL RECOGNITION PARTICLE, 72-KD	AD	MDS, aplastic anemia, pancytopenia
TERC[36–42]	TELOMERASE RNA COMPONENT	AD	Dyskeratosis Congenita (DC): AML, MDS, BMF, head and neck squamous cell carcinoma, anogenital cancers
TERT[36,38,39,41–44]	TELOMERASE REVERSE TRANSCRIPTASE	AD	Dyskeratosis Congenita (DC): AML, MDS, BMF, head and neck squamous cell carcinoma, anogenital cancers
		AR	Hoyeraal-Hreidarsson (HH) syndrome
TP53[45–50]	CELLULAR TUMOR ANTIGEN P53	AD	Li-Fraumeni syndrome (LFS): breast cancer, sarcoma, brain cancer, hematologic malignancies, adrenocortical carcinoma, among others**

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
ALL – Acute lymphoblastic leukemia
AML – Acute myeloid leukemia
AR – Autosomal recessive
BMF – Bone marrow failure
CGH – Comparative genomic hybridization
CML – Chronic myeloid leukemia
MDS – Myelodysplastic syndrome
MLPA – Multiplex ligation-dependent probe amplification

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