

## Hereditary Myeloid Neoplasms Panel, Sequencing

While the majority of myelodysplastic syndromes (MDSs), myeloid neoplasms, and malignancies occur sporadically due to somatic mutations, a portion are due to inherited or hereditary predispositions. Identification of an inherited predisposition can affect therapy options and surveillance strategies, as well as lead to testing of biological relatives, and inform stem cell transplant donor selection. Individuals with an inherited predisposition to myeloid neoplasms may present at a younger age, have more than one first-degree relative with MDS/acute myeloid leukemia (AML), and/or a family history of physical findings associated with a known cancer predisposition syndrome. The preferred specimen type to assess the germline status of patients suspected of, or at risk for, a hereditary predisposition to myeloid neoplasms is cultured skin fibroblasts in order to exclude somatic variants and to avoid false negatives due to peripheral blood somatic mosaicism. ARUP will perform culturing services for skin samples at an additional charge.

### Disease Overview

#### Symptoms/Associated Disorders

- Pathogenic germline variants in several genes have been associated with familial MDS and acute leukemias.
  - Inherited myeloid neoplasm predisposition genes included in this panel that often do NOT present with cytopenia, dysplasia, or other organ dysfunction prior to myeloid malignancy:
    - *CEBPA*
    - *DDX41*
  - Inherited myeloid neoplasm predisposition genes included in this panel that often DO present with preexisting cytopenia(s) or other organ dysfunction prior to myeloid malignancy:
    - *ANKRD26*
    - *ETV6*
    - *GATA2*
    - *RUNX1*
    - *SAMD9*
    - *SAMD9L*
    - *SRP72*
  - Inherited myeloid neoplasm predisposition genes that also predispose to other solid tumors/cancers or syndromic findings:
    - *ATM*
    - *BLM*
    - *CBL*
    - *GATA1*
    - *KRAS*
    - *NBN*
    - *PTPN11*
    - *TP53*
  - Inherited bone marrow failure genes:
    - *ELANE*
    - *TERC*
    - *TERT*
- For a complete list of genes and associated disorders, please see the [Genes Tested](#) table.

### Tests to Consider

#### [Hereditary Myeloid Neoplasms Panel, Sequencing 3001842](#)

**Method:** Massively Parallel Sequencing

Regions of low coverage and reported variants are confirmed by Sanger sequencing as necessary

#### Indication for Testing

- Assesses for inherited/germline DNA variants associated with familial myeloid dysplasias and malignancies
- NOT intended to detect somatic variants
  - To assess somatic DNA variants of diagnostic, prognostic and/or therapeutic significance, order [Myeloid Malignancies Mutation Panel by Next Generation Sequencing, 2011117](#)
- Cultured skin fibroblasts are the preferred sample type to assess the germline status of patients suspected of a hereditary predisposition to myeloid neoplasms
- ARUP will perform culturing services for skin samples at an additional charge

#### [Familial Mutation, Targeted Sequencing 2001961](#)

**Method:** Polymerase Chain Reaction/Sequencing

#### Indication for Testing

- Recommended test for a known familial sequencing variant previously identified in a family member
- A copy of the affected family member's test result documenting the familial variant is required



## Epidemiology

- In the general population, MDS and AML occur in approximately 4.5 and 3.7 per 100,000 individuals, respectively.<sup>1</sup>
- MDS is rare in children and young adults; approximately 50% of childhood MDS is associated with an inherited cause.<sup>2</sup>

## Inheritance

Variable, see [Genes Tested](#) table

## Test Description

See [Genes Tested](#) table for genes included in this panel.

## Clinical Sensitivity

Variable, dependent on phenotype/condition

- Pathogenic germline genetic variants have been identified in approximately 18% of families with hereditary MDS/acute leukemia or other hematologic malignancy.<sup>3,4</sup>

## Contraindications for Ordering

- Should not be ordered to detect somatic variants associated with malignancy because sensitivity for mosaic variants is low with methodology used for germline assays.
- Individuals with hematological malignancy and/or a previous allogeneic bone marrow transplant should not undergo molecular genetic testing on a peripheral blood specimen. Testing of cultured skin fibroblasts is required for accurate interpretation of test results.
- When a relative has a previously identified germline pathogenic variant, see [Familial Mutation, Targeted Sequencing](#).

## Limitations

- A negative result does not exclude a diagnosis of cancer nor a heritable form of myeloid neoplasm.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of the test result may be impacted if the patient has had an allogeneic stem cell transplantation.
- This assay is not intended to detect somatic variants associated with hematologic malignancy, although such variants may be detected.
- This assay cannot definitively distinguish the germline or somatic origin of detected variants when the patient has a hematologic malignancy, and the assay was performed on blood or other tissue that may be contaminated by malignant cells. In such instances, confirmation of germline variant status by testing of cultured skin fibroblasts is strongly recommended.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted gene(s)
  - Regulatory region and deep intronic variants, unless specifically targeted for their clinical relevance
  - Large deletions/duplications in the targeted genes
  - Noncoding transcripts
  - The following exons are not sequenced due to technical limitations of the assay:
    - *ANKRD26* (NM\_014915) exon 19
    - *PTPN11* (NM\_002834) exon 9
    - *SRP72* (NM\_006947) exon 19
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Some variants due to technical limitations in the presence of pseudogenes, or repetitive or homologous regions
  - Low-level somatic variants, including those that have undergone somatic reversion

## Analytical Sensitivity

Variant Class	Analytical Sensitivity (PPA) Estimate <sup>a</sup> (%)	Analytical Sensitivity (PPA) 95% Credibility Region <sup>a</sup> (%)
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<sup>a</sup>Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants



Variant Class	Analytical Sensitivity (PPA) Estimate <sup>a</sup> (%)	Analytical Sensitivity (PPA) 95% Credibility Region <sup>a</sup> (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	99.9	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	99.9	62.1-100

<sup>a</sup>Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

## Genes Tested

Gene	MIM Number	Inherited Disorder, Hematological Disease Associations, Cancer Predispositions	Inheritance
<i>ANKRD26</i> <sup>5</sup>	610855	<i>ANKRD26</i> -related thrombocytopenia MDS Leukemia	AD
<i>ATM</i> <sup>6,7</sup>	607585	Ataxia-telangiectasia Leukemia Lymphoma	AR
		Breast cancer Pancreatic cancer	AD
<i>BLM</i> <sup>8</sup>	604610	Bloom syndrome Leukemia Lymphoma Increased frequency of sister-chromatid exchanges (SCEs)	AR
<i>CBL</i>	165360	Juvenile myelomonocytic leukemia (JMML) Noonan syndrome-like disorder	AD
<i>CEBPA</i> <sup>9</sup>	116897	<i>CEBPA</i> -associated AML	AD
<i>DDX41</i> <sup>10</sup>	608170	Adult onset MDS/AML, with or without macrocytosis or other cytopenias Chronic myeloid leukemia (CML) Non-Hodgkin or Hodgkin lymphoma	AD
<i>ELANE</i> <sup>11</sup>	130130	<i>ELANE</i> -related neutropenia Congenital or cyclic neutropenia Severe or recurrent infections	AD
<i>ETV6</i> <sup>12,13</sup>	600618	MDS/AML Thrombocytopenia Red cell macrocytosis	AD

AD, autosomal dominant; AR, autosomal recessive; X-LR, X-linked recessive



Gene	MIM Number	Inherited Disorder, Hematological Disease Associations, Cancer Predispositions	Inheritance
<i>GATA1</i> <sup>14</sup>	305371	<i>GATA1</i> -related x-linked cytopenia Thrombocytopenia and/or platelet dysfunction Anemia Mild beta thalassemia Neutropenia Congenital erythropoietic porphyria (CEP)	X-LR
<i>GATA2</i> <sup>15,16</sup>	137295	MDS/AML Cytopenias Chronic myelomonocytic leukemia (CMML) Frequent infections/immunodeficiency Pulmonary alveolar proteinosis Lymphedema Sensorineural hearing loss	AD
<i>KRAS</i> <sup>17,18</sup>	190070	Noonan syndrome Cardiofaciocutaneous (CFC) syndrome Costello syndrome JMML	AD
<i>NBN</i> <sup>7,19</sup>	602667	Nijmegen breakage syndrome (NBS) Aplastic anemia Acute lymphoblastic leukemia (ALL)	AR
		Breast cancer	AD
<i>PTPN11</i> <sup>18</sup>	176876	Noonan syndrome LEOPARD syndrome JMML Metachondromatosis	AD
<i>RUNX1</i>	151385	Familial platelet disorder with associated myeloid malignancy (FPDMM) MDS/AML Thrombocytopenia	AD
<i>SAMD9</i>	610456	MIRAGE Syndrome MDS sometimes accompanied by loss of chromosome 7	AD
		Normophosphatemic familial tumoral calcinosis (NFTC)	AR
<i>SAMD9L</i> <sup>20,21</sup>	611170	<i>SAMD9L</i> -related ataxia-pancytopenia syndrome (ATXPC) MDS/leukemia associated with monosomy 7 Somatic revertant mosaicism associated with milder disease Cerebellar ataxia Immunodeficiency	AD



Gene	MIM Number	Inherited Disorder, Hematological Disease Associations, Cancer Predispositions	Inheritance
<i>SRP72</i>	602122	MDS Aplastic anemia/bone marrow failure Hearing loss	AD
<i>TERC</i> <sup>22</sup>	602322	Dyskeratosis congenita Aplastic anemia/bone marrow failure Shortened telomeres Pulmonary fibrosis Somatic revertant mosaicism reported	AD
<i>TERT</i> <sup>22</sup>	187270	Dyskeratosis congenita MDS/AML Aplastic anemia/bone marrow failure Shortened telomeres Cutaneous malignant melanoma Pulmonary fibrosis	AD
		Dyskeratosis congenita (severe)	AR
<i>TP53</i> <sup>7,23</sup>	191170	Li-Fraumeni syndrome (LFS) Leukemia Multiple solid tumors (sarcoma, breast, brain)	AD

AD, autosomal dominant; AR, autosomal recessive; X-LR, X-linked recessive

## References

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## Additional Resources

Desai AV, Perpich M, Godley LA. [Clinical assessment and diagnosis of germline predisposition to hematopoietic malignancies: The University of Chicago Experience](#). Front Pediatr. 2017;5:252. PubMed

## Related Information

[Acute Myeloid Leukemia - AML](#)  
[Myelodysplastic Syndromes](#)

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