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

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 Targeted Sequencing 3005867**

**Method:** Massively Parallel Sequencing

- Testing for a known familial sequence variant by sequencing gene of interest. A copy of the family member's test result documenting the familial gene variant is REQUIRED.
- To determine if the variant(s) of interest are detectable by this assay, contact an ARUP genetic counselor at 800-242-2787.
Inherited bone marrow failure genes:
- *ELANE*
- *TERC*
- *TERT*

For a complete list of genes and associated disorders, please see the **Genes Tested** table.

**Epidemiology**

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

**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.³⁴

**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 allogenic 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.

**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

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

*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

<table>
<thead>
<tr>
<th>Gene</th>
<th>MIM Number</th>
<th>Inherited Disorder, Hematological Disease Associations, Cancer Predispositions</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANKRD26</td>
<td>610855</td>
<td>ANKRD26-related thrombocytopenia MDS Leukemia</td>
<td>AD</td>
</tr>
<tr>
<td>ATM</td>
<td>607585</td>
<td>Ataxia-telangiectasia Leukemia Lymphoma</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast cancer Pancreatic cancer</td>
<td></td>
</tr>
<tr>
<td>BLM</td>
<td>604610</td>
<td>Bloom syndrome Leukemia Lymphoma</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased frequency of sister-chromatid exchanges (SCEs)</td>
<td></td>
</tr>
<tr>
<td>CBL</td>
<td>165360</td>
<td>Juvenile myelomonocytic leukemia (JMML) Noonan syndrome-like disorder</td>
<td>AD</td>
</tr>
<tr>
<td>CEBPA</td>
<td>116897</td>
<td>CEBPA-associated AML</td>
<td>AD</td>
</tr>
<tr>
<td>DDX41</td>
<td>608170</td>
<td>Adult onset MDS/AML, with or without macrocytosis or other cytopenias Chronic myeloid leukemia (CML) Non-Hodgkin or Hodgkin lymphoma</td>
<td>AD</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive; X-LR, X-linked recessive
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<tr>
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<th>Inheritance</th>
</tr>
</thead>
</table>
| ELANE  | 130130     | ELANE-related neutropenia
Congenital or cyclic neutropenia
Severe or recurrent infections                                                                                                           | AD          |
| ETV6   | 600618     | MDS/AML
Thrombocytopenia
Red cell macrocytosis                                                                                                                      | AD          |
| GATA1  | 305371     | GATA1-related x-linked cytopenia
Thrombocytopenia and/or platelet dysfunction
Anemia
Mild beta thalassemia
Neutropenia
Congenital erythropoietic porphyria (CEP)                                                                                                    | X-LR        |
| GATA2  | 137295     | MDS/AML
Cytopenias
Chronic myelomonocytic leukemia (CMML)
Frequent infections/immunodeficiency
Pulmonary alveolar proteinosis
Lymphedema
Sensorineural hearing loss                                                                                                                    | AD          |
| KRAS   | 190070     | Noonan syndrome
Cardiofaciocutaneous (CFC) syndrome
Costello syndrome
JMML                                                                                                                                             | AD          |
| NBN    | 602667     | Nijmegen breakage syndrome (NBS)
Aplastic anemia
Acute lymphoblastic leukemia (ALL)                                                                                                            | AR          |
|        |            | Breast cancer                                                                                                                                          | AD          |
| PTPN11 | 176876     | Noonan syndrome
LEOPARD syndrome
JMML
Metachondromatosis                                                                                                                             | AD          |
| RUNX1  | 151385     | Familial platelet disorder with associated myeloid malignancy (FPDMM)
MDS/AML
Thrombocytopenia                                                                                                                             | AD          |
| SAMD9  | 610456     | MIRAGE Syndrome
MDS sometimes accompanied by loss of chromosome 7                                                                                           | AD          |

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<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normophosphatemic familial tumoral calcinosis (NFTC)</td>
<td>AR</td>
</tr>
<tr>
<td><em>SAMD9L</em></td>
<td>20,21</td>
<td>Dyskeratosis congenita-related ataxia-pancytopenia syndrome (ATXPC)</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MDS/leukemia associated with monosomy 7</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Somatic revertant mosaicism associated with milder disease</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Cerebellar ataxia</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Immunodeficiency</td>
<td></td>
</tr>
<tr>
<td>SRP72</td>
<td>602122</td>
<td>MDS</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aplastic anemia/bone marrow failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hearing loss</td>
<td></td>
</tr>
<tr>
<td>TERC</td>
<td>602322</td>
<td>Dyskeratosis congenita</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aplastic anemia/bone marrow failure</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Shortened telomeres</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Pulmonary fibrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Somatic revertant mosaicism reported</td>
<td></td>
</tr>
<tr>
<td>TERT</td>
<td>187270</td>
<td>Dyskeratosis congenita</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MDS/AML</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aplastic anemia/bone marrow failure</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Shortened telomeres</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cutaneous malignant melanoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary fibrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyskeratosis congenita (severe)</td>
<td>AR</td>
</tr>
<tr>
<td>TP53</td>
<td>7,23</td>
<td>Li-Fraumeni syndrome (LFS)</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leukemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple solid tumors (sarcoma, breast, brain)</td>
<td></td>
</tr>
</tbody>
</table>

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References


Additional Resources


Related Information

Acute Myeloid Leukemia - AML
Myelodysplastic Syndromes