This panel is specifically designed to diagnose the most common genetic causes of bone marrow failure including dyskeratosis congenita, Diamond Blackfan anemia, Fanconi anemia, familial bone marrow failure, Shwachman Diamond syndrome and congenital amegakaryocytic thrombocytopenia, as well as inherited causes of neutropenia. Inherited bone marrow failure syndromes account for approximately 25% of pediatric patients and about 10% of young adult patients who present with aplastic anemia. Inherited bone marrow failure syndromes are caused by mutations in many different genes, and may be inherited as autosomal dominant, autosomal recessive, or X-linked disorders.

Malignant transformation is a significant risk for individuals with many of these disorders; thus, accurate and timely diagnosis is crucial for appropriate medical surveillance and management.

**Test Offerings:**

**Bone marrow failure syndromes 59 gene panel by NGS**

Sub-panels are available for specific conditions:
- Dyskeratosis congenita 8 gene panel
- Diamond Blackfan anemia 12 gene panel
- Fanconi anemia 16 gene panel
- Inherited neutropenia 21 gene panel

**Indications:**

- Confirmation of genetic diagnosis in a patient with a clinical diagnosis of bone marrow failure or associated syndrome
- Carrier or presymptomatic diagnosis identification in individuals with a family history of bone marrow failure of unknown genetic basis.

**Gene Specific or Sub-panel Sequencing:**

- Confirmation of genetic diagnosis in a patient with bone marrow failure and in whom a specific genetic diagnosis is suspected.
Mutation Specific Analysis:

- Presymptomatic testing of at-risk siblings and parents for medical management and prior to bone marrow donation
- Carrier identification in individuals in whom specific mutation(s) have been identified in the proband with bone marrow failure
- Prenatal diagnosis of an at-risk fetus, after confirmation of mutation(s) in the parent(s) and by prior arrangement only.

Specimen:

At least 3-5 mLs whole blood in a lavender top (EDTA) tube.

Note: Saliva samples are required for analysis in patients who have undergone bone marrow transplantation and may facilitate DNA isolation in patients undergoing chemotherapy or in individuals with leukopenia. Please call 513-636-4474 for a free saliva collection kit.

Testing Methodology:

Bone Marrow Failure Syndromes Panel by NGS:

This test is performed by enrichment of the exons, flanking intronic and un-translated regions (5’ and 3’) of the genes specified above using microdroplet PCR technology followed by next-generation sequencing. All pathogenic and novel variants, as well as variants of unknown significance, as determined bioinformatically, are confirmed by Sanger sequencing. Additional Sanger rescue sequencing may be undertaken, if indicated.

Gene Specific Sequencing/ Mutation Specific Analysis:

Sanger sequencing following PCR amplification of the specified coding and exon/intron boundaries of the specified gene.

Sensitivity:

Clinical Sensitivity: Approximately 90% of FA patients have at least one mutation that is identifiable by this test. Approximately 50% of patients with classic dyskeratosis congenita have an identifiable mutation in one of the genes on this panel. Approximately 55% of patients with a diagnosis of Diamond Blackfan anemia have a genetic mutation identifiable by sequencing. Biallelic mutations in the SBDS are found in approximately 80% of individuals who meet the diagnostic criteria for Shwachman Diamond syndrome. Approximately 95% of patients with CAMT have identifiable biallelic mutations in MPL.

At least 70-80% of the genetic causes of congenital or inherited neutropenia are identified by this panel. Approximately 60% of North American patients with severe congenital neutropenia have a mutation in ELANE; as do approximately 90% of patients with cyclic neutropenia. Mutations in HAX1, G6PC3, GFI1, WAS and CSF3R account for 10-20% of patients collectively. Over 90% of patients with Barth syndrome have mutations in TAZ; approximately 2/3 of which can be detected by this test. Only 35% of patients with Cohen syndrome have mutations in VPS13B, but nearly all patients who have Cohen syndrome with neutropenia have an identifiable mutation. Approximately 90% of patients with a clinical diagnosis of Chediak- Higashi syndrome have mutations that are identifiable by this test. Approximately 80% of patients with GATA2 deficiency will have identifiable mutations. The clinical sensitivities of remaining rare causes of genetically determined bone marrow failure syndromes are not known.

Analytical Sensitivity: The sensitivity of NGS is approximately 99% for the detection of nucleotide base changes, small deletions and insertions in the regions analyzed. Somatic mutations are likely to be detected when they are present in >20% of cells analyzed. Mutations in regulatory regions or other untranslated regions are not detected by this test. Large deletions involving entire single exons or multiple exons are especially common in this group of disorders, perhaps accounting for up to 20% of all mutations, and will not be identified using this test methodology. Deletion and duplication analysis may be indicated as a follow up test in symptomatic patients with normal or heterozygous results.

Note: Targeted deletion and duplication analysis of every gene on this panel except FANCD2, RPL15, RPS17, and SBDS is clinically available at an additional charge.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Inheritance</th>
<th>Condition</th>
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<tbody>
<tr>
<td>AP3B1</td>
<td>AR</td>
<td>Hermansky Pudlak type 2</td>
</tr>
<tr>
<td>BRCA2 (FANCD1), BRIP1 (FANCl), ERCC4 (FANCC), FANC, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, PALB2 (FANCN), RAD51C (FANCO), SLX4 (FANCP)</td>
<td>AR; except FANCB- XR</td>
<td>Fanconi anemia</td>
</tr>
<tr>
<td>CSF3R</td>
<td>AD, AR and somatic</td>
<td>Severe congenital neutropenia (germline); predisposition to MDS (somatic)</td>
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<tr>
<td>CXCR4</td>
<td>AD</td>
<td>WHIM syndrome</td>
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<tr>
<td>DKC1</td>
<td>XR</td>
<td>Dyskeratosis congenita or Hoyeraal Hreidarsson syndrome</td>
</tr>
<tr>
<td>ELANE (ELA2)</td>
<td>AD</td>
<td>SCN1</td>
</tr>
<tr>
<td>GATA1</td>
<td>X linked</td>
<td>GATA1-related X-linked cytopenia</td>
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<tr>
<td>GATA2</td>
<td>AD</td>
<td>GATA2 deficiency</td>
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<tr>
<td>GFI1</td>
<td>AD</td>
<td>SCN2</td>
</tr>
<tr>
<td>HAX1</td>
<td>AR</td>
<td>SCN3, Kostmann syndrome</td>
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<tr>
<td>LAMTOR2 (ROBLD3)</td>
<td>AR</td>
<td>p14 deficiency</td>
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<tr>
<td>LYST</td>
<td>AR</td>
<td>Chediak Higashi syndrome</td>
</tr>
<tr>
<td>MPL</td>
<td>AR</td>
<td>Congenital amegakaryocytic thrombocytopenia</td>
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<tr>
<td>NHP2 (NOLA2)</td>
<td>AR</td>
<td>Dyskeratosis congenita</td>
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<tr>
<td>NOP10 (NOLA3)</td>
<td>AR</td>
<td>Dyskeratosis congenita</td>
</tr>
<tr>
<td>RAB27A</td>
<td>AR</td>
<td>Griscelli syndrome type 2</td>
</tr>
<tr>
<td>RAC2</td>
<td>AR</td>
<td>Neutrophil immunodeficiency syndrome</td>
</tr>
<tr>
<td>RFL5, RPL11, RPL15, RPL26, RPL35A, RPS7, RPS10, RPS17, RPS19, RPS24, RPS26</td>
<td>AD</td>
<td>Diamond Blackfan anemia</td>
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<tr>
<td>RTEL1</td>
<td>AD and AR</td>
<td>Dyskeratosis congenita</td>
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<tr>
<td>SBDS</td>
<td>AR</td>
<td>Shwachman Diamond syndrome (SDS)</td>
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<tr>
<td>SLC37A4</td>
<td>AR</td>
<td>Glycogen storage disease type IB</td>
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<td>SRP72</td>
<td>AD</td>
<td>Familial bone marrow failure syndrome</td>
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<tr>
<td>TAZ</td>
<td>X linked</td>
<td>Barth syndrome</td>
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<tr>
<td>TERC (hTR)</td>
<td>AD</td>
<td>Dyskeratosis congenita</td>
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<tr>
<td>TERT</td>
<td>AD and AR</td>
<td>Dyskeratosis congenita</td>
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<tr>
<td>TINF2</td>
<td>AD</td>
<td>Classic or severe DC, Revesz syndrome, Hoyeraal Hreidarsson syndrome; AD 3</td>
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<tr>
<td>USB1</td>
<td>AR</td>
<td>Clericuzio-type poikiloderma with neutropenia</td>
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<tr>
<td>VPS13B</td>
<td>AR</td>
<td>Cohen syndrome; congenital neutropenia with retinopathy</td>
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<tr>
<td>VPS45</td>
<td>AR</td>
<td>SCN5</td>
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<tr>
<td>WAS</td>
<td>X linked</td>
<td>Wiskott Aldrich syndrome, X-linked</td>
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<tr>
<td>WRAP53 (TCAB1, WDR79)</td>
<td>AR</td>
<td>Dyskeratosis congenita, Revesz syndrome, Hoyeraal Hreidarsson syndrome</td>
</tr>
</tbody>
</table>
Turn-Around Time:
• Bone Marrow Failure Syndromes Panel by NGS: 42 days
• Single Gene Sequencing: 28-84 days
• Deletion and duplication analysis: 30 days

CPT Codes:
• Bone Marrow Failure NGS Panel: 81479x52, 81406x4, 81408, 81405, 81216
• Single Gene sequencing of any gene on this panel except BRCA2 (FANCD1), PALB2 (FANCN), RPS19, SLC37A4, TAZ, VPS13B or WAS 81479
• Single Gene sequencing of PALB2 (FANCN), SLC37A4, TAZ, or WAS 81406
• Single Gene sequencing of BRCA2 (FANCD1) 81216
• Single Gene sequencing of VPS13B 81408
• Single Gene sequencing of RPS19 81405
• Deletion/duplication analysis of single gene except FANCD2, RPL15, RPS17, SBDS, VPS13B and BRCA2 (FANCD1) 81479
• Deletion/duplication analysis of VPS13B 81407
• Deletion/duplication analysis of BRCA2 (FANCD1) 81213
• Deletion and duplication analysis of BMFS panel (55 genes) 81479(x53), 81213, 81407
• Family specific study: 81403

Please call 1-866-450-4198 for current pricing, insurance preauthorization or with any billing questions.

Results: Results will be reported to the referring physician or health care provider as specified on the test requisition.

Shipping Instructions
Please enclose test requisition with sample. All information must be completed before sample can be processed. Place samples in Styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday.

Ship to:
Cytogenetics and Molecular Genetics Laboratories
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474

References: