Bone Marrow Failure Syndromes Panel by next-generation sequencing (NGS)

Genes Tested

MPL	*RPL5*	*RPL11*	*RPL35A*
RPS7	*RPS10*	*RPS17*	*RPS19*
RPS24	*RPS26*	*SBDS*	

Description: Inherited bone marrow failure syndromes account for approximately 25% of pediatric patients and about 10% of young adults who present with aplastic anemia. Bone marrow failure syndromes can be caused by mutations in many different genes and may be inherited in autosomal dominant, autosomal recessive or X-linked recessive manners.

Diamond-Blackfan Anemia (DBA) is caused by defects of ribosome biogenesis. DBA is chiefly characterized by macrocytic anemia with normal leukocytes and platelets in a patient less than 1 year. Growth retardation and congenital anomalies are common features of the disease. Approximately 30% to 50% of patients have congenital malformations of the limbs, head and face, heart or genitourinary system. Individuals with DBA are at increased risk of developing hematopoetic malignancies including acute myeloid leukemia and as well as solid tumors including osteogenic sarcoma.

Shwachman Diamond syndrome (SDS) is a severe genetic disorder characterized by exocrine pancreatic dysfunction, bone abnormalities, hematologic abnormalities including neutropenia or multi-lineage cytopenia and predisposition towards myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML). It is the second most common cause of congenital exocrine pancreatic insufficiency after cystic fibrosis. However, pancreatic dysfunction can improve with age and may not be present in older patients. Neonates with SDS are typically asymptomatic but present within the first year of life with failure to thrive and poor growth due to pancreatic insufficiency and recurrent infections secondary to neutropenia. Malignant transformation is a significant risk in individuals with SDS.

Congenital amegakaryocytic thrombocytopenia (CAMT or AMEGA) is characterized by isolated thrombocytopenia and megakaryocytopenia in the absence of other physical anomalies. Patients with CAMT are at risk of developing aplastic anemia and leukemia later in life.

Genetics: **DBA** is inherited as an autosomal dominant disease with high variability and expressivity among affected family members. Once a DBA mutation is identified in a family, genetic testing of other at-risk family members is critical for their appropriate medical management.

Both **CAMT** and **SDS**, secondary to mutations in *MPL* and *SBDS* respectively, are inherited as autosomal recessive disorders. Genetic testing of at-risk siblings early in life is recommended in order to plan for their appropriate medical care as well as to identify potential bone marrow donors for symptomatic siblings.

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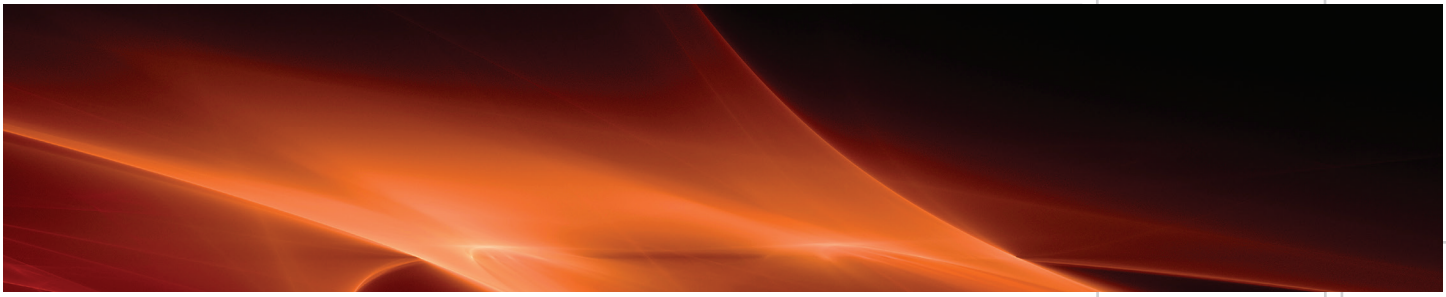

Indications:

Confirmation of diagnosis in a patient with the following symptoms:

- Bone marrow failure of unknown etiology in a pediatric or young adult patient
- Congenital anomalies consistent with one of these diagnoses
- History of leukemia, lymphoma or solid tumor at an earlier than expected age, particularly in association with other features of bone marrow failure syndrome
- Pancreatic dysfunction and/or neutropenia.

Specimen: At least 5 mLs whole blood in a lavender top (EDTA) tube. Label tube with patient's name, birth date, and date of collection.

Testing Methodology: 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 with > 40 fold coverage at every target base. All pathogenic and novel variants, as well as variants of unknown (indeterminate) significance, as determined bioinformatically, are confirmed by Sanger sequencing.

Sensitivity:

Clinical Sensitivity: Approximately 50% of patients with a diagnosis of DBA have a mutation identifiable by sequencing. Approximately 95% of patients with CAMT have identified biallelic mutations in *MPL*. Biallelic mutations in *SBDS* are identified in approximately 80% of individuals who meet the diagnostic criteria for SDS. Deletion/duplication analysis may be indicated as a follow-up test in symptomatic patients with a normal NGS sequencing result or a single (heterozygous) mutation in *MPL* or *SBDS*.

Sensitivity continued:

Analytical Sensitivity: The sensitivity of DNA sequencing is over 99% for the detection of nucleotide base changes, small deletions and insertions in the regions analyzed. Mutations in regulatory regions or other untranslated regions are not detected by this test. Large deletions involving entire single exons or multiple exons, large insertions and other complex genetic events have been reported in many of these genes and will not be identified using this test methodology. Rare primer site variants may lead to erroneous results.

Note: Single gene sequencing is available for all genes in the panel.

Turn-Around Time:

- Up to 12 weeks for NGS of the panel
- 4-12 weeks for analysis of any gene by Sanger sequencing

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

CPT Codes:

- Bone Marrow Failure Panel by NGS 81479x10, 81405
- Single gene sequencing of any gene in this panel 81479

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

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Congenital amegakaryocytic thrombocytopenia

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