Diamond Blackfan Anemia Panel by next-generation sequencing (NGS)

**Disorder:**

Diamond Blackfan anemia (DBA) is an inherited bone marrow failure syndrome caused by defects of ribosome biogenesis. DBA is chiefly characterized by infantile or early childhood onset red cell anemia, although growth retardation and congenital malformations are common features. 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 hematopoietic malignancies as well as solid tumors, including acute myeloid leukemia and osteogenic sarcoma. The phenotypic spectrum of Diamond Blackfan anemia is broad, and symptoms can vary markedly between affected individuals, even between family members. X-linked thrombocytopenia with or without anemia and secondary to mutations in GATA1 is included in this panel because of its phenotypic overlap with DBA.

**Genetics:**

Diamond Blackfan anemia is a genetically heterogeneous disorder, and is inherited in an autosomal dominant pattern. Approximately 45% of cases are inherited from an affected parent and 55% are isolated cases. DBA is an incompletely penetrant disease. Therefore, some mutation-positive family members do not meet diagnostic criteria, but may be at increased risk of developing malignancies. GATA1 mutations segregate in an X-linked semi-dominant manner.

**Genes Tested:**

<table>
<thead>
<tr>
<th>GATA1</th>
<th>RPL5</th>
<th>RPL11</th>
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<tbody>
<tr>
<td>RPL15</td>
<td>RPL26</td>
<td>RPL35A</td>
</tr>
<tr>
<td>RPS7</td>
<td>RPS10</td>
<td>RPS17</td>
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<tr>
<td>RPS19</td>
<td>RPS24</td>
<td>RPS26</td>
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</table>

**Indications:**

Diamond Blackfan Anemia Panel by NGS

Confirmation of diagnosis in a patient with the following symptoms:

- Classic DBA: normochromic macrocytic anemia in the absence of other cytopenias, reticulocytopenia, normal marrow cellularity with a paucity of erythroid precursors, age less than one year
- Non-classic DBA: macrocytosis, elevated erythrocyte adenosine deaminase activity, or elevated HbF with mild or absent anemia, short stature or congenital anomalies consistent with DBA, adult onset of symptoms of DBA.

**Gene Specific Sequencing:**

- Confirmation of genetic diagnosis in a patient with DBA and in whom a specific genetic diagnosis is suspected.

**Mutation Specific Analysis:**

- Presymptomatic testing of at-risk family members for medical management and prior to bone marrow donation
- Prenatal diagnosis of an at-risk fetus (by prior arrangement only).

**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:**

Diamond Blackfan Anemia 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 with > 20 fold coverage at every target base. All pathogenic and novel variants, as...
well as variants of unknown significance, as determined bioinformatically, are confirmed by Sanger sequencing.

**Gene Specific Sequencing/ Mutation Specific Analysis:** Sanger sequencing following PCR amplification of the specified coding and exon/intron boundaries of the specified gene.

**Test Sensitivity:**

**Clinical Sensitivity:** Approximately 55% of patients with DBA have an identifiable mutation in one of the 12 genes listed above. Mutations in RPS19 are identified in approximately 25% of patients with DBA, while mutations in RPL5, RPS10 and RPS11 account for approximately 5% of cases each. Few patients have been described with mutations in the remaining DBA genes.

**Note:** Sequence analysis of RPS29 is not included in this panel but is available through Custom Gene Sequencing (see website for details).

**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. 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 is recommended as a follow up test when Diamond Blackfan Anemia Panel by NGS results are normal and the index of clinical suspicion remains high.

**Note:** Targeted deletion and duplication analysis of every gene on this panel except RPS17 and RPL15 is clinically available at an additional charge.

**CPT Codes:**

- Fanconi Anemia Panel by NGS: 81216, 81406, 81479 (x14)
- Diamond Blackfan Anemia Panel by NGS: 81479x11, 81405
- Single gene sequencing of any gene on this panel except RPS19: 81479
- Single gene sequencing of RPS19: 81405
- Deletion/duplication analysis of single gene (except RPL15 and RPS17): 81479
- Deletion and duplication analysis of entire panel (except RPL15 and RPS17): 81479x10
- Mutation specific analysis: 81403

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

**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

**Results:**

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


