Diamond-Blackfan anemia (DBA) is an inherited red blood cell aplasia disorder associated with reduced or absent erythroid precursors in bone marrow, macrocytic anemia and reticulocytopenia [1]. Approximately 30% of cases have growth retardation and 50% have congenital anomalies, which may include thumb anomalies, congenital heart defects and midline facial defects such as cleft palate and hypertelorism [1]. Patients have an increased risk of malignancies, including acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and solid tumors such as osteogenic sarcoma [1]. The cumulative incidence of solid tumors or leukemia is 22% by age 46 [2]. DBA is a genetically heterogeneous condition, with the currently known genes accounting for 50-70% of cases [1]. All the DBA genes included on this panel are inherited in an autosomal dominant manner. An estimated 55-60% of cases are caused by de novo mutations; DBA has variable expressivity and penetrance is incomplete.

Our Diamond-Blackfan Anemia Sequencing Panel includes sequence analysis of all 11 genes listed below. Our Diamond-Blackfan Anemia Deletion/Duplication Panel includes deletion/duplication analysis of 8 genes listed in bold below.

### Diamond-Blackfan Anemia Sequencing Panel

<table>
<thead>
<tr>
<th>Gene</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>GATA1</td>
<td>Patients with inherited thrombocytopenia in a concurrent hemolytic anemia should raise the suspicion of thrombocytopenia caused by GATA1 mutations or sitosterolemia [3]. Recent exome sequencing has identified a novel splice site mutation in GATA1 in two siblings with DBA [4].</td>
</tr>
<tr>
<td>RPL5</td>
<td>DBA type 6, caused by heterozygous mutations in RPL5, is typically associated with multiple physical anomalies, including craniofacial, thumb and cardiac anomalies [5].</td>
</tr>
<tr>
<td>RPL11</td>
<td>Heterozygous mutations in RPL11 are associated with DBA type 7. In terms of observed congenital malformations, mutations in RPL11 are predominantly associated with isolated thumb defects [5].</td>
</tr>
<tr>
<td>RPL15</td>
<td>Deletions of RPL15 have been identified in patients with Diamond-Blackfan anemia recently [6, 7].</td>
</tr>
<tr>
<td>RPL26</td>
<td>Gazda HT et al. (2012) identified a frameshift mutation in p53 regulator RPL26 that is associated with multiple physical abnormalities and a specific pre-ribosomal RNA processing defect in diamond-blackfan anemia[8].</td>
</tr>
<tr>
<td>RPL35A</td>
<td>Mutations in RPL35A have been identified in both familial and sporadic cases of DBA type 5. In one familial case, some individuals were found to have subclinical DBA with macrocytic anemia [9].</td>
</tr>
<tr>
<td>RPS7</td>
<td>RPS7 has been associated with DBA type 8 [10]. At least one individual with no associated physical anomalies has been described [5].</td>
</tr>
<tr>
<td>RPS10</td>
<td>RPS10 mutations are associated with DBA type 9, and are estimated to account for 2.6% of all DBA cases [11].</td>
</tr>
<tr>
<td>RPS19</td>
<td>Mutations in the RPS19 gene account for an estimated 24% of all DBA cases overall [12].</td>
</tr>
<tr>
<td>RPS24</td>
<td>RPS24 mutations are associated with DBA type 3, and account for an estimated 2% of DBA cases [13]. Both sporadic and familial mutations have been described [13].</td>
</tr>
<tr>
<td>RPS26</td>
<td>Mutations in RPS26 are associated with DBA type 10, and account for an estimated 6.4% of DBA cases overall. Based on available data from a limited number of cases, physical malformations appear to be rare in patients with RPS26 mutations [11].</td>
</tr>
</tbody>
</table>

### Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Deletion/duplication analysis of the panel genes is performed by oligonucleotide array-CGH. Partial exonic copy number changes and
rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

**Diamond-Blackfan Anemia Sequencing Panel (sequence analysis of 11 genes)**

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube. NOTE: blood samples are not accepted if patient has a history of MDS or leukemia. Please send 2 T-25 flasks of cultured skin fibroblasts instead.

Cost: $2000

CPT codes: 81407

Turn-around time: 8 weeks

*Note: We cannot bill insurance for the Diamond-Blackfan Anemia panel*

**Diamond-Blackfan Anemia Deletion/Duplication Panel (deletion/duplication analysis of 8 genes)**

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube. NOTE: blood samples are not accepted if patient has a history of MDS or leukemia. Please send 2 T-25 flasks of cultured skin fibroblasts instead.

Cost: $1545

CPT codes: 81406

Turn-around time: 4-6 weeks

**Results:**

Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. One report will be issued for the entire Diamond-Blackfan Anemia Sequencing Panel. All abnormal results are reported by telephone or email.

*For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.*

**References:**