Clinical Features and Molecular Genetics:
The familial occurrence of myelodysplastic syndrome (MDS) and/or acute leukemia (AL) is rare and heterogeneous. Some families inherit purely AL, and others inherit purely MDS or both disorders within the same pedigree. Many cases of familial MDS/AL also arise in those with particular genetic syndromes with additional clinical findings. Patients with familial MDS/AL are usually younger at presentation than individuals with sporadic disease and are recognized by an unusual family history of more than one first-degree relative with MDS/AL. Most of the families show a pattern of inheritance consistent with a single gene mutation, inherited in an autosomal dominant manner [1, 2].

Our Comprehensive Familial Myelodysplastic Syndrome/Acute Leukemia includes sequence analysis of all 28 genes and deletion/duplication analysis of 23 genes listed below.

<table>
<thead>
<tr>
<th>Tier 1: Familial MDS/AL Panel</th>
<th>Tier 2: Familial MDS/AL Panel</th>
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<tbody>
<tr>
<td>ANKRD26</td>
<td>CEBPA</td>
</tr>
<tr>
<td>IKZF1*</td>
<td>PAX5</td>
</tr>
<tr>
<td>SAMD9L*</td>
<td>SRP72</td>
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*Genes are not included in deletion/duplication analysis.

Tier 1: Familial Myelodysplastic Syndrome/Acute Leukemia Panel (Pure familial MDS/AL)
Pure familial MDS/AL is characterized by multiple cases of MDS and/or AL without bone marrow failure or other phenotypic features in one family. It is due to inheritance of a single abnormal copy of a gene encoding a transcription factor that is critical for hematopoiesis [1]. Mutation carriers can have additional findings in addition to the clinical features than MDS/AL, but these may be subtle or absent [1].

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<td>ANKRD26</td>
<td>AD</td>
<td>Mutations in the 5’UTR and protein coding regions of ANKRD26 were reported to cause an autosomal-dominant form of inherited thrombocytopenia, THC2. It has been reported that among 105 people with confirmed or suspected ANKRD26 mutations, 10 developed hematologic malignancies, including seven with acute leukemias. The overall incidence of development of hematologic malignancies was 240 out of 100,000, and of acute leukemia was 167 out of 100,000, both elevated over expected levels [3-5].</td>
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<td>CEBPA</td>
<td>AD</td>
<td>Mutations in the CEBPA gene are associated with familial acute myeloid leukemia (AML). Typically the first mutation present in the germline within the 5’ end of the gene, and a second 3’ mutation is acquired within the leukemia. Though germline 3’ CEBPA mutations have also been identified, CEBPA mutations confer a relatively favorable prognosis. Patients found to have biallelic CEBPA mutations within their leukemic cells should be tested for germline mutations [6].</td>
</tr>
<tr>
<td>GATA2</td>
<td>AD</td>
<td>Germline mutations in GATA2 have been described in association with familial MDS/AML, as well as with several heterogeneous clinical syndromes, including Emberger syndrome and the MonoMAC syndrome which show an overall increased risk of developing MDS/AML [6, 7]. Although the incidence of MDS/AL appears very high, there is incomplete penetrance, with some individuals living into late adulthood without developing malignancy or demonstrating hematologic or infectious abnormalities [1].</td>
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<td>Approximately 10% of patients with ataxia telangiectasia due to biallelic ATM mutations develop cancer, mostly of the lymphoid malignancies including Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, and several forms of leukemia [30, 31]. AML has also been reported in patients with AT [32, 33].</td>
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<td>BLM (RECQL3)</td>
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<td>Mutations in the gene encoding DNA helicase RecQ protein-like-3 (BLM) cause Bloom syndrome. A 13%-25% lifetime risk of MDS/AML has been reported in patients with Bloom syndrome [19, 29].</td>
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<td>Germline mutations in BRCA1 increase the risks of breast or ovary cancer and many other types of cancer, including myeloid leukemia [34-36].</td>
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<td>Germline mutations in BRCA2 predispose individual to a number of different cancers, including leukemia [34-36].</td>
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<td>CBL</td>
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<td>Germline mutations of the CBL gene are associated with CBL syndrome with predisposition to juvenile myelomonocytic leukemia [37].</td>
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**Tier 2: Familial Myelodysplastic Syndrome/Acute Leukemia Panel**

- **ATM** (Autosomal Recessive)
- **BLM (RECQL3)** (Autosomal Recessive)
- **BRCA1** (Autosomal Dominant)
- **BRCA2** (Autosomal Dominant)
- **CBL** (Autosomal Dominant)

**Clinical Features and Molecular Pathology**

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<td>CHEK2 (CHK2)</td>
<td>AD</td>
<td>Li-Fraumeni syndrome, which can be caused by an inherited germline mutation in the CHEK2 tumor suppressor gene, presents with an increased risk of nearly all malignancies, including leukemias [2, 29].</td>
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<td>MLH1 MSH2 MSH6 PMS2</td>
<td>AR/AD</td>
<td>Heterozygous mutations in MLH1, MSH2, MSH6 and PMS2 are associated with hereditary nonpolyposis colon cancer (HNPCC), which is associated with an increased risk of certain cancers, particularly colon and ovarian cancers. Homozygous or compound heterozygous mutations in these genes lead to a mismatch repair deficiency that can result in a mutator phenotype characterized by early onset gastrointestinal tumors, leukemia and/or lymphoma and features of neurofibromatosis type 1. These features can be summarized with the acronym CoLoN’ (Colon tumors or/and Leukemia/Lymphoma or/and Neurofibromatosis features) [38-40].</td>
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<td>NBN (NBS1)</td>
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<td>Biallelic mutations in the NBS1 gene are responsible for the Nijmegen breakage syndrome which display an elevated risk to lymphoblastic leukemia [39].</td>
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<td>NF1</td>
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<td>NF1 microdeletions are associated with a more severe neurofibromatosis 1 (NF1) phenotype and increased risk for developing malignant tumors, including leukemias (especially juvenile myelomonocytic leukemia, with a risk of progression toward AML) [41, 42].</td>
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<td>PTPN11</td>
<td>AD</td>
<td>PTPN11 mutations are the most common cause of Noonan syndrome, and cause 90% of LEOPARD syndrome cases[43]. Patients with Noonan syndrome and LEOPARD syndrome have a predisposition for leukemia and certain solid tumors [44-46]. Noonan syndrome and a pathogenic PTPN11 mutation represents a 3.5 times increased risk of developing a cancer compared with the general population[46].</td>
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**Testing Options**

**Comprehensive Familial Myelodysplastic Syndrome/Acute Leukemia Panel (sequencing analysis of all 28 genes and deletion/duplication analysis of 23 genes)**

- **Sample specifications:**
  - 2 T-25 flasks of cultured skin fibroblasts, or DNA extracted from fibroblasts. NOTE: Peripheral blood samples are not accepted for patients with a history of MDS/leukemia.
  - **Cost:** $4000
  - **CPT codes:** 81406, 81407
  - **Turn-around time:** 4-6 weeks

*Note: We cannot bill insurance for this test.*

**Tier 1: Familial Myelodysplastic Syndrome/Acute Leukemia Panel (sequencing analysis of 15 genes and deletion/duplication analysis of 10 genes)**

- **Sample specifications:**
  - 2 T-25 flasks of cultured skin fibroblasts, or DNA extracted from fibroblasts. NOTE: Peripheral blood samples are not accepted for patients with a history of MDS/leukemia.
  - **Cost:** $3500
  - **CPT codes:** 81406, 81407
  - **Turn-around time:** 4-6 weeks

*Note: We cannot bill insurance for this test.*

**Tier 2: Familial Myelodysplastic Syndrome/Acute Leukemia Panel (sequence and deletion/duplication analysis of 13 genes)**

- **Sample specifications:**
  - 2 T-25 flasks of cultured skin fibroblasts, or DNA extracted from fibroblasts. NOTE: Peripheral blood samples are not accepted for patients with a history of MDS/leukemia.
  - **Cost:** $2000
  - **CPT codes:** 81406, 81407
  - **Turn-around time:** 4-6 weeks

*Note: We cannot bill insurance for this test.*

**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.
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 panel. All abnormal results are reported by telephone.

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

References:


Committed to CUSTOMIZED DIAGNOSTICS, TRANSLATIONAL RESEARCH & YOUR PATIENTS’ NEEDS