Inherited Bone Marrow Failure Syndrome (IBMFS) Testing

MOL.TS.360.A
v2.0.2021

Introduction

Inherited bone marrow failure syndrome (IBMFS) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedures addressed by this guideline</th>
<th>Procedure codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBMFS Multigene panel</td>
<td>81479</td>
</tr>
</tbody>
</table>

What are inherited bone marrow failure syndromes

Definition

Bone marrow failure (BMF) is the inability of the bone marrow to produce a sufficient quantity of functional blood cells to meet physiologic demands.1 BMF is typically classified into three categories, based on presumed etiology: inherited, secondary, or idiopathic.1 Inherited bone marrow failure syndromes (IBMFSs) are a group of genetically defined disorders that are characterized by BMF. Individuals presenting with aplastic anemia (AA), myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and chronic unexplained cytopenias should be evaluated for an IBMFS.1

Incidence

"The incidence of inherited bone marrow failures accounts for 10% to 15% of marrow aplasia and 30% of pediatric bone marrow failure disorders with approximately 65 cases per million live births every year."2 Seventy-five percent of children with an IBMFS have an identifiable cause.2
Symptoms

While specific features may vary by each type of IBMFS, features that are present in most IBMFSs include bone marrow failure with single or multi-lineage cytopenia. Many individuals have an increased risk to develop aplastic anemia (AA), myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and solid malignancies.\(^1\)\(^3\)

IBMFSs typically present with specific patterns of cytopenias, and an individual with an IBMFS may have congenital anomalies and other characteristic physical features or health issues.\(^1\)

Phenotypic overlap between IBMFSs makes it difficult to establish a diagnosis based solely on clinical features.\(^3\)

IBMFSs typically present within the first decade of life; however, delay in diagnosis and variability in phenotypic spectrum may lead to diagnosis into adulthood.\(^3\)

Cause

“A wide variety of specific syndromes have been described so far with more than 80 different genes associated to IBMFSs. Based on the inheritance patterns of IBMFSs in multiplex families and the segregation of mutated alleles in known IBMFS genes of phenotypically affected family members, the disorders are considered monogenic in the vast majority of patients.”\(^4\)

Inheritance

IBMFSs may be inherited in an autosomal dominant (AD), autosomal recessive (AR), or X-linked (XL) manner, depending on the gene involved.

Diagnosis

The diagnosis of an IBMFS is suspected based on hematopoietic test results, physical features, and family history.

Timely genetic testing is essential to establish a diagnosis in the individual and to guide appropriate management, treatment, and cancer surveillance.\(^3\) Additionally, knowing the genetic cause in the individual allows for genetic testing in family members. This information is important for their own health and a critical part of their workup if being considered as a possible bone marrow transplant donor.

The risk of development of cancers differs greatly between the various IBMFSs, and identification of the underlying etiology of marrow failure is imperative to assess the need and type of cancer screening.\(^4\)

Treatment

Treatment of IBMFSs varies depending on the specific type, but typically involves supportive care, including blood and/or specific blood cell transfusions, and in severe situations, hematopoietic stem cell transplants (HSCTs).
Survival

The survival range of IBMFSs varies across the multiple conditions included in this group. Survival is impacted by disease severity, response to initial therapy, and the age at the time of initial transplant. The overall survival for individuals with an IBMFS is also significantly impacted by the development of MDS, with disease progression occurring 4.7 months from the time of MDS diagnosis.

Note For additional information on specific IBMFSs, their causes and common presentations and symptoms, see the table at the end of this document titled Select Inherited Bone Marrow Failure Syndromes.

Test information

Introduction

The investigation and diagnosis of individuals with IBMFSs necessitates a combination of laboratory analyses (including complete blood counts with differential, telomere length studies, exocrine pancreatic function studies, bone marrow analysis, and cytogenetic studies), along with clinical assessment and genetic testing. Clinical genetic testing is available for many IBMFSs, via known familial mutation analysis, single gene analysis and/or multi-gene panels.

Multigene Panel Testing

Until recently, most sequencing tests used the Sanger sequencing methodology that was originally developed in the 1970s. Sanger sequencing is labor intensive and did not lend itself to high-throughput applications.

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. NGS may not perform as well as Sanger sequencing in some applications.

NGS tests vary in technical specifications (e.g., depth of coverage, extent of intron/exon boundary analysis, methodology of large deletion/duplication analysis).

Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions.
Results may be obtained that cannot be adequately interpreted based on the current knowledgebase. When a sequence variation is identified that has not been previously characterized or shown to cause the disorder in question, it is called a variant of uncertain significance (VUS). VUSs are relatively common findings when sequencing large amounts of DNA with NGS.

Under certain circumstances, technologies used in multi-gene testing may fail to identify mutations that might be identifiable through single-gene testing. If high clinical suspicion exists for a particular syndrome, testing for that syndrome should be performed instead of a broad multi-gene panel.

**Guidelines and evidence**

**Introduction**

The following section includes relevant guidelines and evidence pertaining to inherited bone marrow failure syndrome genetic testing. Although there are no current U.S. guidelines address the use of multi-gene panels in IBMFSs, there are guidelines published for a subset of IBMFSs.

**Dyskeratosis Congenita**

Guidelines for diagnosis and management of dyskeratosis congenita (DC) were published by expert authors in consultation with a medical advisory board in 2015:

- "Individuals should be considered to have DC if they have telomere lengths below the first percentile for age by multicolor flow cytometry with fluorescent in situ hybridization (flow FISH) in several subsets of leukocytes (granulocytes, CD45+ naïve T cells, CD45-memory T cells, CD20+ B cells, CD57+ NK/NKT cells) or a damaging or deleterious mutation in a DC associated gene."

**Fanconi Anemia**

The Fanconi Anemia Research Fund Inc. held a consensus conference in 2013 in which experts established guidelines for diagnosis and management of Fanconi anemia (FA):

- "Patients with FA may present with AA, MDS, single cytopenias, or macrocytic red cells without another explanation. A diagnosis of FA should be considered in all children and young adults with androgen-responsive or ATG/cyclosporine A-non-responsive "acquired" aplastic anemia. It is absolutely imperative to test for FA if a stem cell transplant is planned, as standard stem cell transplant conditioning will result in significant morbidity and high mortality rates for patients with FA."

- "The first test that should be used to diagnose FA is the chromosome breakage test, which is performed on a sample of the patient’s blood in a clinical cytogenetics laboratory."
• “If the results from the chromosome breakage test are positive, then mutation analysis should be performed to identify the specific genetic mutation that has caused the patient to develop FA.”

• Recommendations for follow-up testing are made based on the results of the chromosome breakage studies:
  
  o Negative: No further testing for FA unless strong clinical suspicion.
  
  o Positive: Next-generation sequencing for known FA genes followed by copy number evaluation for deletions/duplications if not captured on original panel and no mutations are identified in gene panel.

  o Equivocal:

    ▪ Next-generation sequencing or targeted mutation testing for other chromosome instability/DNA repair syndromes

    ▪ Skin chromosome breakage study (if not already performed)

**Shwachman-Diamond Syndrome**

Draft consensus guidelines for the diagnosis and treatment of Shwachman-Diamond Syndrome (SDS) were published in 2011:¹

• “The clinical diagnosis is established by (a) documenting evidence of characteristic exocrine pancreatic dysfunction and hematological abnormalities and (b) excluding known causes of exocrine pancreatic dysfunction and bone marrow failure. Attention should be given to ruling out cystic fibrosis (the most common cause of pancreatic insufficiency) with a sweat chloride test, Pearson disease (pancreatic insufficiency and cytopenia, marrow ring sideroblasts and vacuolated erythroid and myeloid precursors), cartilage hair hypoplasia (diarrhea and cytopenia, and metaphyseal chondrodysplasia, and more common in certain isolated populations such as the Amish), and other inherited bone marrow failure syndromes (such as dyskeratosis congenita)."

• “As the clinical diagnosis of SDS is usually difficult and patients may present at a stage when no clinical pancreatic insufficiency is evident, it is advisable to test most or all suspected cases for mutations in the SBDS gene. It is noteworthy that about 10% of patients with clinical features of SDS do not have identifiable mutations, and that de novo SBDS mutations have been identified in some families."

**Selected Relevant Publications**

An expert-authored review (2017) states the following regarding IBMFSs:¹

• “Genetic testing is an indispensable tool in the diagnostic evaluation of IBMFSs that complements traditional clinical history, examination, and laboratory evaluation, especially in the setting of overlapping or adult presentations. However, clinical use of this powerful tool is currently limited by cost or access in most places."
• "In addition, even when genetic testing is available, it may fail to provide the correct diagnosis." This is because not all genes that cause IBMFS have been identified, many rare variants in known IBMFS genes cannot currently be classified as disease causing, or in the event of somatic reversion, the genetic variant(s) that cause a patient's IBMFS may not be detectable in peripheral blood cells.
• "Now and likely well into the future, the sum of all available tools is greater than any alone, and a modern IBMFS workup should include a focused history and physical examination, screening tests, and genetic evaluation whenever possible."

Criteria

Introduction

This guideline applies to inherited bone marrow failure syndrome multi-gene panels, which are defined as assays that simultaneously test for more than one inherited bone marrow failure gene.

IBMFS Multigene Panel

• Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing:
  - No previous testing of the requested genes, and
  - No known IBMFS pathogenic variant in the family or
  - If there is a known IBMFS pathogenic variant in the family, testing has been performed and is negative, and a diagnosis of IBMFS is still suspected, AND

• The member has or is suspected to have a condition that will benefit from information provided by the requested IBMFS gene testing based on at least one of the following:
  - The member meets all criteria in a test-specific guideline, if available, or
  - The following criteria are met:
    - The member displays clinical features of the condition for which testing is being requested:
      - unexplained chronic cytopenia with or without associated congenital physical anomalies consistent with the condition, or
      - sporadic aplastic anemia, or
      - myelodysplastic syndrome, or
• lack of cytopenias but classic physical findings, cancer diagnosis, or family history, and

  ▪ Acquired etiologies have been considered and ruled out when possible (e.g., immune-mediated or viral), and
  ▪ Predicted impact on health outcomes, including immediate impact on medical management based on the molecular results, and
  ▪ Member’s clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing is available, and
  ▪ Family and medical history do not point to a specific genetic diagnosis or pattern of inheritance for which a more focused test or panel would be appropriate, and
  ▪ The member does not have a known underlying cause for their symptoms (e.g. known genetic condition), AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy.

---

**Note** Alternative sample, such as DNA from a skin biopsy, may need to be considered in a patient with MDS/AML and/or when there is concern for somatic reversion events.¹

---

**Billing and reimbursement considerations**

The billed amount should not exceed the list price of the test.

If clinical screening tests are indicative of a specific IBMFS, a smaller multi-gene panel that contains condition specific genes will be reimbursed (i.e. Fanconi Anemia gene panel).

Germline genetic testing is only necessary once per lifetime. Therefore, a single gene included in a panel or a multi-gene panel may not be reimbursed if testing has been performed previously. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.

This guideline may not apply to genetic testing for indications that are addressed in test-specific guidelines. Please see the test-specific list of guidelines for a complete list of test-specific panel guidelines.

If a panel was previously performed and an updated, larger panel is being requested, only testing for the medically necessary, previously untested genes will be reimbursable. Therefore, only the most appropriate procedure codes for those additional genes will be considered for reimbursement.

When multiple CPT codes are billed for components of a panel and there is a more appropriate CPT code representing the panel, eviCore will redirect to an appropriate panel code(s).
If the laboratory will not accept redirection to a single code, the medical necessity of each billed component procedure will be assessed independently using the criteria above for single gene testing. Only the individual panel components that meet medical necessity criteria as a first tier of testing will be reimbursed. The remaining individual components will not be reimbursable.

**Table: Select Inherited Bone Marrow Failure Syndromes**

<p>| Note | Familial myelodysplastic syndrome is an inherited form of the usually sporadic myelodysplastic syndrome (MDS).&lt;sup&gt;8,10&lt;/sup&gt; It does not have non-hematologic findings and may be caused by many of the genes listed in the table below. Familial MDS is associated with dysplastic changes in the bone marrow, cytopenias, and an increased risk to develop AML. All inheritance patterns have been described, depending on the causative gene identified. |</p>
<table>
<thead>
<tr>
<th>Syndrome Name</th>
<th>Hematologic &amp; malignancy risks</th>
<th>Other features</th>
<th>Diagnosis</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital amegakaryocytic thrombocytopenia (CAMT)</td>
<td>Isolated thrombocytopenia due to ineffective megakaryocytopenia at birth, with elevated plasma TPO levels. Progression to pancytopenia/plastic anemia will occur in the majority of affected individuals. Individuals are at risk to develop MDS and AML. Genotype-phenotype correlations exist and individuals with type I variants have earlier progression to bone marrow failure than those with type II.</td>
<td>N/A</td>
<td>Identification of mutations in MPL.</td>
<td>AR</td>
</tr>
<tr>
<td>Syndrome Name</td>
<td>Hematologic &amp; malignancy risks</td>
<td>Other features</td>
<td>Diagnosis</td>
<td>Inheritance</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------------------------</td>
<td>---------------</td>
<td>-----------</td>
<td>-------------</td>
</tr>
</tbody>
</table>
| Diamond-Blackfan anemia (DBA)<sup>13,14</sup> | Classic: characterized by profound normochromic and typically macrocytic anemia. Elevated erythrocyte adenosine deaminase (eADA) activity levels are elevated in the majority of individuals with DBA. 90% of affected individuals will experience red cell aplasia within the first year of life. Other individuals have very mild anemia, requiring no treatment. There is an increased risk to develop AML, MDS, and solid tumors such as osteosarcoma. | Approximately 25-50% of individuals with DBA will have congenital malformations including thumb malformations, craniofacial anomalies, and congenital heart disease; 30% will have growth retardation. | DBA is suspected in individuals who meet the following diagnostic criteria:  
• Age <1 year  
• Macrocytic anemia with no other significant cytopenias  
• Reticulocytopenia  
• Normal marrow cellularity with a paucity of erythroid precursors | Usually AD GATA1- and TSR2-related DBA are XL |
<table>
<thead>
<tr>
<th>Syndrome Name</th>
<th>Hematologic &amp; malignancy risks</th>
<th>Other features</th>
<th>Diagnosis</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fanconi Anemia (FA)(^{15})</td>
<td>At increased risk for progressive BMF with pancytopenia, usually in first decade, and increased risk for solid tumors (squamous cell cancers of the head, neck, and anogenital region). Carriers of a subset of FA-related genes (e.g., BRCA2, PALB2, and BRIP1) have an increased risk for breast and other cancers.</td>
<td>Physical features are present in ~75% of individuals. Growth deficiency, abnormal skin pigmentation, skeletal malformations of the upper and lower limbs (especially thumbs), microcephaly, ophthalmic anomalies, and genitourinary tract anomalies.</td>
<td>Increased chromosome breakage and radial forms induced by diepoxybutane (DEB) and mitomycin C. Fanconi Anemia is caused by a mutation or mutations in one of the following genes: BRCA2, BRIP1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, ERCC4, FANCL, FANCM, MAD2L2, PALB2, RAD51, RAD51C, RFWD3, SLX4, UBE2T, XRCC2.</td>
<td>Usually AR. AD (RAD51 gene) and XL (FANCB gene) cases have been reported.</td>
</tr>
<tr>
<td>Syndrome Name</td>
<td>Hematologic &amp; malignancy risks</td>
<td>Other features</td>
<td>Diagnosis</td>
<td>Inheritance</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>GATA2 deficiency$^{16,17}$</td>
<td>Cytopenias, myelodysplasia. Individuals have an increased risk to develop MDS and leukemias (AML and CMML). The majority of cases in the pediatric population who develop MDS will have monosomy 7 on bone marrow karyotype.</td>
<td>Viral and bacterial infections, pulmonary alveolar proteinosis and lymphedema.</td>
<td>Identification of a mutation in GATA2. &quot;GATA2 mutations have been found in up to 10% of those with congenital neutropenia and/or aplastic anemia.&quot;</td>
<td>AD</td>
</tr>
<tr>
<td>Syndrome Name</td>
<td>Hematologic &amp; malignancy risks</td>
<td>Other features</td>
<td>Diagnosis</td>
<td>Inheritance</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>SAMD9-related MIRAGE and SAMD9L-ATXPC syndromes.(^{18,19})</td>
<td>SAMD9: myelodysplasia and SAMD9L: cytopenia and predisposition to marrow failure with risk of MDS. Both syndromes are associated with monosomy 7 on bone marrow biopsy. These syndromes are likely underdiagnosed due to a common occurrence of genetic reversion to restore hematopoiesis.</td>
<td>SAMD9: MIRAGE (myelodysplasia, infection, restriction of growth, adrenal hyperplasia, genital phenotypes, and enteropathy) syndrome SAMD9L: cerebellar ataxia</td>
<td>Identification of a mutation in SAMD9 or SAMD9L.</td>
<td>AD</td>
</tr>
<tr>
<td>Severe congenital neutropenia (SCN) (^{1,20})</td>
<td>A &quot;chronic state of severe neutropenia associated with a neutrophil count less than 500/uL lasting longer than 3 months, often presenting in the first year of life.&quot; At increased risk of MDS and AML.</td>
<td>Severe/recurrent infections, dental issues (chronic gingivitis and caries), decreased bone mineral density.</td>
<td>Identification of mutation or mutations in one of the following genes: HAX1, ELANE, AK2, GF11, CSF3R, WAS, G6PC3.</td>
<td>AD, AR, and XL.</td>
</tr>
<tr>
<td>Syndrome Name</td>
<td>Hematologic &amp; malignancy risks</td>
<td>Other features</td>
<td>Diagnosis</td>
<td>Inheritance</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------------</td>
<td>---------------</td>
<td>-----------</td>
<td>-------------</td>
</tr>
<tr>
<td>Shwachman-diamond syndrome (SDS)&lt;sup&gt;21-23&lt;/sup&gt;</td>
<td>Single or multi-lineage cytopenias. At increased risk for MDS and AML.</td>
<td>Exocrine pancreatic dysfunction with gastrointestinal malabsorption, malnutrition and growth failure.</td>
<td>Diagnosis can be established when exocrine pancreatic dysfunction and bone marrow dysfunction are present. Identification of mutation or mutations in one of the following genes: SBDS, ELF1, DNAJC21, SRP54.</td>
<td>Usually AR. Some AD (SRP54 gene) cases have been reported.</td>
</tr>
<tr>
<td>Syndrome Name</td>
<td>Hematologic &amp; malignancy risks</td>
<td>Other features</td>
<td>Diagnosis</td>
<td>Inheritance</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------------</td>
<td>----------------</td>
<td>-----------</td>
<td>-------------</td>
</tr>
<tr>
<td>Telomere biology disorders(^{24-27}) (Dyskeratosis congenita (DC); TERC/TERT-related disorders)</td>
<td>At increased risk for BMF, MDS, AML, and solid tumors.</td>
<td>DC: Classic triad of nail dysplasia, lacy reticular pigmentation of the upper chest/and or back, and oral leukoplakia. Infants: IUGR, cerebellar hypoplasia, immunodeficiency and retinopathy. TERC/TERT: Eye abnormalities, dental abnormalities, developmental delay, short stature, microcephaly, and genitourinary abnormalities. Pulmonary fibrosis is the most common presentation of a telomere biology disorder and may be the only symptom in adults.</td>
<td>DC: Identification of mutation or mutations in one of the following genes: ACD, CTC1, DKC1, NHP2, NOP10, PARN, RTEL1, TINF2, WRAP53. TERC/TERT: Identification of mutation or mutations in the TERC or TERT genes. Approximately 70% of individuals with a clinical diagnosis are found to have a mutation or mutations in an associated gene.</td>
<td>AD, AR, and XL.</td>
</tr>
</tbody>
</table>
References

Introduction

These references are cited in this guideline.


