Inherited Bone Marrow Failure Syndromes (IBMFS) Genetic Testing Policy

Effective Date: August 28, 2024

Executive Summary:

This health insurance policy focuses on using genetic testing, specifically multi-gene panels, to diagnose and manage Inherited Bone Marrow Failure Syndromes (IBMFS). These are a group of genetic disorders that affect the bone marrow's ability to produce blood cells, leading to conditions like aplastic anemia, myelodysplastic syndromes (MDS), and acute myeloid leukemia (AML). People with IBMFS have a higher risk of developing serious illnesses and cancers.

Multi-gene panel testing is important for diagnosing IBMFS because it allows doctors to look at multiple genes at once. This is helpful because the symptoms of IBMFS can be similar to each other, making it hard to diagnose based on symptoms alone. Accurate genetic diagnosis helps doctors provide better care and treatment for patients, and it can also help identify family members who might be at risk, which is important for their health and for finding potential bone marrow donors.

The policy ensures that genetic testing is only done when necessary and includes genetic counseling before and after the test to help patients understand the process and make informed decisions.

By including genetic testing in the diagnosis, this policy aims to improve patient outcomes, help doctors make better treatment decisions, and reduce healthcare costs by providing timely and targeted care.

Criteria:

Inherited bone marrow failure syndromes (IBMFS) multi-gene panel testing, defined as assays that simultaneously test for more than one inherited bone marrow failure gene, is considered medically necessary when ALL of the following criteria are met:

1. 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

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2. The patient has or is suspected to have a condition that will likely 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 one of the following clinical features of an IBMFS:
            a) unexplained chronic single- or multi- lineage cytopenia with or without associated congenital physical anomalies, or
            b) sporadic aplastic anemia, or
            c) myelodysplastic syndrome, or
            d) lack of cytopenias but classic physical findings, cancer diagnosis, AND family history, AND

3. Alternate non-genetic etiologies have been considered and ruled out, when possible (e.g., acquired etiologies including immune-mediated or viral), AND

4. The patient does not have a known underlying cause for their symptoms (e.g., known genetic condition).

Background:

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

- While specific features vary by each type of IBMFS, features that are present in most IBMFSs include bone marrow failure with single or multi-lineage cytopenia; many carry an increased risk for development

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of aplastic anemia (AA), myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and solid malignancies.[1,2]
- IBMFSs typically present within the first decade of life; however, delay in diagnosis and variability in phenotypic spectrum may lead to diagnosis even into adulthood.[2]
- IBMFSs have been shown to present with isolated aplastic anemia or myelodysplastic syndrome. An underlying IBMFS diagnosis was identified in 5.1% and 13.6% of presumed sporadic aplastic anemia and MDS cases, respectively.[3]
- Phenotypic overlap between IBMFSs makes it difficult to establish a diagnosis based solely on clinical features.[2]
- 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).
- Clinical management and outcomes in individuals with aplastic anemia and myelodysplastic syndrome differ in those with an underlying IBMFS compared to sporadic disease.[1]
- Timely genetic testing is essential to establish a diagnosis in the proband and to guide appropriate management, treatment, and cancer surveillance.[2] Additionally, knowing the genetic cause in the proband allows for genetic testing in family members. This information is important for their own health and a critical part of their workup if they are being considered as a possible bone marrow transplant donor.

Some of the most common IBMFSs are summarized below:
- **Fanconi Anemia (FA) – FA** is a disorder that is typically inherited in an autosomal recessive manner, though X-linked and autosomal dominant forms have been reported. Heterozygotes (carriers) are not at risk for FA. However, carriers of a subset of FA-related genes (e.g., *BRCA2*, *PALB2*, and *BRIP1*) have an increased risk for breast and other cancers.[4] FA is characterized by BMF and increased risk for malignancy. Physical abnormalities are present in ~75% of individuals and include growth deficiency, abnormal skin pigmentation, skeletal malformations of the upper and lower limbs (especially thumbs), microcephaly, ophthalmic anomalies, and genitourinary tract anomalies. Progressive BMF with pancytopenia is typically present in the first decade of life. Additional solid tumor malignances include squamous cell cancers of the head, neck, and anogenital region. Diagnosis of FA can be established in an individual with increased chromosome breakage and radial forms induced by diepoxybutane (DEB) and mitomycin C.

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Molecular testing can confirm the diagnosis with identification of pathogenic variant(s). [4]

- **Telomere biology disorders (TBD) –** Dyskeratosis congenita (DC) is the most common telomere biology disorder and is inherited in X-linked, autosomal dominant, or autosomal recessive manner. DC is caused by defective telomere maintenance and characterized by a classic triad of nail dysplasia, lacy reticular pigmentation of the upper chest and/or back, and oral leukoplakia, though this triad may not present until adolescence or adulthood.[5] Other TBD include Hoyeraal-Hreidarsson (HH) syndrome, Revesz Syndrome, and Coats Plus Syndrome. In HH, infants may be severely affected with history of intrauterine growth restriction, cerebellar hypoplasia, immunodeficiency and retinopathy[6]. Other physical features in TBD may include eye abnormalities, dental abnormalities, developmental delay, short stature, microcephaly, and genitourinary anomalies. It is recognized that there is a broad phenotypic spectrum ranging from mild to severe. The TBD family have overlapping involved disease genes. Individuals with a telomere biology disorder are at increased risk for BMF, MDS, AML, solid tumors, pulmonary fibrosis, and liver cirrhosis. Pulmonary fibrosis is the most common presentation of a telomere biology disorder, and may be the only symptom in adults.[7] Approximately 70% of individuals with a clinical diagnosis are found to have a pathogenic variant(s) in an associated gene.[5]
- **Shwachman-Diamond syndrome (SDS) –** SDS is a disorder most commonly inherited in an autosomal recessive fashion though some autosomal dominant cases have been reported. SDS is characterized by exocrine pancreatic dysfunction with gastrointestinal malabsorption, malnutrition and growth failure.[8] Individuals may also experience single or multi-lineage cytopenias and are at an increased risk for MDS and AML. A broad phenotypic spectrum has been recognized. Myers *et al*. found that only 19/37 patients with genetically confirmed SDS presented with the classical combination of features. [9] Diagnosis can be established in an individual with the classic findings of exocrine pancreatic dysfunction and bone marrow dysfunction and/or by identification of pathogenic variant(s) in the *SBDS, ELF1, DNAJC21* or *SRP54* genes. [10]
- **Diamond-Blackfan anemia (DBA) –** DBA is a disorder typically inherited in an autosomal dominant manner, though *GATA1*- and *TSR2*-related DBA are inherited in an X-linked manner.[11] Classical DBA is characterized by profound normochromic and typically macrocytic anemia. Approximately 25-50% of individuals with DBA will have

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congenital malformations including thumb malformations, craniofacial anomalies, and congenital heart disease; 30% will have growth retardation. Ninety percent of affected individuals will experience red cell aplasia within the first year of life. Other individuals have very mild anemia, requiring no treatment[11]. While less commonly than other IBMFSs, DBA does have an increased risk of development of AML, MDS, and solid tumors such as osteosarcoma. DBA is suspected in individuals who meet the following diagnostic criteria:

1. Age younger than one year
2. Macrocytic anemia with no other significant cytopenias
3. Reticulocytopenia
4. Normal marrow cellularity with a paucity of erythroid precursors

Erythrocyte adenosine deaminase activity (eADA) levels are elevated in the majority of individuals with DBA.[12] Genetic analysis of the 21 genes known to be associated with DBA will identify a pathogenic variant in ~65% of affected individuals.[11]

- **Severe congenital neutropenia (SCN) –** SCN is a "chronic state of severe neutropenia associated with a neutrophil count less than 500/μL lasting longer than 3 months, often presenting in the first year of life."[1] SCN's can be associated with different features, which typically include severe/recurrent infections, dental issues (chronic gingivitis and caries), decreased bone mineral density, and increased risk for MDS/AML. The most well-described SCN disorders are caused by pathogenic variants in the *HAX1* and *ELANE* genes. Additional pathogenic variants have been reported in *AK2, GF11*, *CSF3R, WAS, JAGN1,* and *G6PC3*. Autosomal dominant, autosomal recessive, and X-linked forms have been described.[1,13]
- **Congenital amegakaryocytic thrombocytopenia (CAMT) –** CAMT is a rare autosomal recessive IBMFS associated with pathogenic variants in *MPL*. CAMT is characterized by isolated thrombocytopenia due to ineffective megakaryocytopoiesis at birth, with elevated plasma thrombopoietin (TPO) levels.[14] Thrombocytopenia will progress to pancytopenia/aplastic anemia in the majority of affected individuals. Individuals are at risk to develop MDS and AML.[14,15] Genotype-phenotype correlations exist, and individuals with type I variants have earlier progression to bone marrow failure than those with type II.[14]

Hematologic neoplasms can also be associated with germline predisposition; these neoplasms typically include myelodysplastic syndromes (MDS) and AML. MDS is a heterogeneous group of disorders characterized by dysplastic changes in the bone marrow, cytopenias, and an increased risk of developing

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AML. MDS is primarily a sporadic disease that occurs in older individuals, but inherited forms have been described. Familial MDS disorders are inherited in an autosomal dominant manner.[16,17] Such inherited forms have associated syndromes as below:

- **GATA2 deficiency –** GATA2 deficiency is an autosomal dominant disorder caused by pathogenic variants in the *GATA2* gene. GATA2 deficiency results in a range of phenotypes including viral and bacterial infections, cytopenias, myelodysplasia, pulmonary alveolar proteinosis and lymphedema. Individuals with GATA2 deficiency have an increased risk to develop MDS and leukemias (AML and chronic myelomonocytic leukemia (CMML)).[18] The majority of pediatric patients who develop MDS will have a monosomy 7 identified by bone marrow karyotype or fluorescence in situ hybridization (FISH). [19]
- ***SAMD9*-related MIRAGE and *SAMD9L*-ATXPC syndromes –** Variants in the *SAMD9* and *SAMD9L* genes cause autosomal dominant IBMFSs. *SAMD9* mutations cause MIRAGE (myelodysplasia, infection, restriction of growth, adrenal hyperplasia, genital phenotypes, and enteropathy) syndrome.[20,21] *SAMD9L* mutations are characterized by cerebellar ataxia, cytopenia and predisposition to bone marrow failure with risk of MDS. Both syndromes are associated with monosomy 7 cytogenetic finding in bone marrow specimen biopsy. These syndromes are likely underdiagnosed due to a common occurrence of genetic reversion to restore hematopoiesis. [22]
- **Hematologic neoplasms associated with germline predisposition without a constitutional disorder affecting multiple organs –** Germline mutations in *DDX41* and *TP53* can predispose to myeloid (AML, MDS), or lymphoid neoplasms. Germline mutations in *CEBPA* predispose to myeloid neoplasms. Germline mutations in *PAX5* or *IKZF1* predispose to B-lymphoblastic leukemia (B-ALL).[23,24,25]
- **Hematologic neoplasms with germline predisposition associated with a constitutional platelet disorder –** Germline *RUNX1* alterations can be associated with lymphoid (T-ALL, B-ALL, mature B-cell lymphomas) or myeloid (Familial platelet disorder with associated myeloid malignancy – FPDMM) disorders, the latter most commonly MDS, AML, or CMML. Germline mutations in *ANKRD26* lead to familial thrombocytopenia and predispose to MDS and AML. Germline alterations in the *ETV6* gene predispose to both myeloid and lymphoid neoplasms including B-ALL, MDS, AML, CMML, and plasma cell myeloma. Non-hematologic neoplasms are also reported including colorectal and breast cancers. [23, 24, 25]

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- **Down Syndrome –** Down syndrome characterized by constitutional trisomy 21 karyotype (or mosaic) predisposes neonates to transient abnormal myelopoiesis, but later AML (usually acute megakaryoblastic leukemia) and B-ALL. [25]
- **Germline RAS activating mutations –** Neurofibromatosis type 1 (germline alterations in *NF1* gene), CBL syndrome (germline mutations in *CBL*), and Noonan syndrome (germline mutations in *PTPN11, KRAS, NRAS*, or *RIT1*) are associated with juvenile myelomonocytic leukemia (JMML) or JMML-like neoplasms. [25]

Technical Information:

The investigation and diagnosis of patients with IBMFSs necessitates a combination of laboratory analyses, including completed blood counts with differential, telomere length studies, exocrine pancreatic function studies, bone marrow analysis, and cytogenetic studies, along with clinical assessment and genetic testing.[1]

Clinical genetic testing is available for many IBMFSs, via single gene analysis and/or multi-gene panels. The efficiency of next generation sequencing (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 making it difficult to reliably narrow down likely causes. As a result, several laboratories have begun to combine genes involved in certain conditions which often have both of those characteristics.

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 remains for a particular syndrome after negative multi-gene test results, consultation with the testing lab and/or additional targeted genetic testing may be warranted.

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

Guidelines and Evidence:

No current U.S. guidelines address the use of multi-gene panels in IBMFSs.

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

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> "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."

There are guidelines published for a subset of IBMFSs that have suggestive laboratory findings in addition to genetic sequencing:

Fanconi Anemia

The Fanconi Anemia Research Fund Inc. established guidelines for diagnosis and management of Fanconi Anemia (FA):[26]

> "The chromosome breakage test, is the first test that should be performed for an individual suspected of having FA. This assay is performed in a clinical cytogenetics laboratory, often using a sample of the patient's peripheral blood. Lymphocytes isolated from the blood sample are treated with DNA cross-linking agents; the most commonly used for FA testing are diepoxybutane (DEB) and mitomycin C (MMC) and the chromosomes are examined for evidence of chromosomal breakage."
>
> "If the results from the chromosome breakage test are positive, genetic testing should be performed to identify the specific pathogenic variants (PV(s)) associated with the patient's FA phenotype. Genetic testing enables accurate diagnosis, which may improve clinical care for individuals with anticipated genotype-phenotype associations and for relatives who are heterozygous carriers of PVs that confer an increased risk for malignancy."

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Recommendations for follow-up testing are made based on the results of the chromosome breakage studies:

- Negative:
  - No further testing for Fanconi anemia unless strong clinical suspicion. If clinical suspicion is high, skin fibroblast testing should be considered. If breakage is not within FA-range, clinical evaluation for other disorders with phenotypic overlap.
- Positive:
  - Genetic counseling. Targeted FA gene panel including sequencing and copy number analysis.
  - If targeted panel negative, whole exome or whole genome sequencing
- Equivocal:
  - Next-generation sequencing for other chromosome instability/DNA repair syndromes.
  - Skin chromosome breakage study (if not already performed)

The guidelines highlight the importance of genetic testing to identify family members who carry the mutation and are at risk for additional health consequences, such as a predisposition to cancer.

Telomere Biology Disorders

Guidelines for diagnosis and management of telomere biology disorders (TBD) :[27]

"The first step in testing for a suspected TBD is to assess the telomere length in specific subtypes of white blood cells. If all or nearly all of the white blood cells' telomere lengths are determined to be very short (less than 1% length for their age), the test result is consistent with diagnosis of TBD. However, it is possible that not all individuals with a TBD will have all very short telomeres."

"Once an individual has been identified to have clinical features and/or telomere lengths that are consistent with or suggestive of a TBD, genetic testing is recommended for TBD-associated genes to try to identify a causative gene variant."

Shwachman-Diamond syndrome

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Draft consensus guidelines for the diagnosis and treatment of SDS were published in 2011:

> "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)."[28]
>
> "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."[28]

Exclusions and Other Considerations:

- Pre- and post-test counseling by an appropriate provider, such as an American Board of Medical Genetics and Genomics or American Board of Genetic Counseling-certified Genetic Counselor, is strongly recommended.
- Deletion/duplication analysis is often performed concurrently on clinically available panels. If deletion/duplication analysis is not performed on initial panel testing or is not comprehensive (i.e., doesn't detect smaller exon deletions) and sequencing is negative, consider sending for deletion/duplication analysis.
- 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]

CPT Codes:

Procedure(s) addressed by this policy:	

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	Procedure Code(s)
IBMFS Multigene panel [Inherited bone marrow failure syndromes (IBMFS) (eg, Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, GATA2 deficiency syndrome, congenital amegakaryocytic thrombocytopenia) sequence analysis panel, must include sequencing of at least 30 genes, including BRCA2, BRIP1, DKC1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, GATA1, GATA2, MPL, NHP2, NOP10, PALB2, RAD51C, RPL11, RPL35A, RPL5, RPS10, RPS19, RPS24, RPS26, RPS7, SBDS, TERT, and TINF2]	81441
Unlisted molecular pathology procedure	81479

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Update details:

All references were reviewed, and additional references were included. Stakeholder feedback from the Insurance Alignment Committee and SCH Lab Stewardship Committee was solicited and incorporated when appropriate. Updated Executive Summary was added.

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