Test Specific Guidelines

Inherited Bone Marrow Failure Syndrome (IBMFS) Testing

MOL.TS.360.A
v1.0.2023

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 is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
Inherited bone marrow failure syndromes (IBMFS) 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
IBMFS Multigene panel	81479

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 and classification of an IBMFS requires a combination of clinical, family history, physical examination, laboratory, and bone marrow findings in addition to specialized testing, such as molecular diagnostics.[5]

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.[6]

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

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.[1] Clinical genetic testing is available for many IBMFSs, via known familial mutation analysis, single gene analysis and/or multi-gene panels.

Multi-Gene Testing Panels

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 making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in patient management, and/or minimize the chance of finding variants of uncertain clinical significance.

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 multigene panels in IBMFSs, there are guidelines published for a subset of IBMFSs.

Fanconi Anemia

The Fanconi Anemia Research Fund Inc. (FARF, 2020) established expert guidelines for diagnosis and management of Fanconi Anemia (FA) which stated:[7]

"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 FA-causing variants. Genetic testing enables accurate diagnosis and improves clinical care for individuals with anticipated genotype/phenotype manifestations and for relatives who are heterozygous carriers of FA gene variants that confer increased risk for malignancy."

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

Negative: No further testing for FA unless strong clinical suspicion.

Positive: Targeted FA gene panel and deletion/duplication analysis.

Equivocal:

Next-generation sequencing 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, 2011) stated:[8]

“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."

Telomere Biology Disorders

Guidelines for diagnosis and management of telomere biology disorders (TBD) were published by expert authors in consultation with a medical advisory board in 2022:[9]

"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 the causative gene variant."

Selected Relevant Publications

An expert-authored review (2017) stated 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.

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

Note **Familial myelodysplastic syndrome is an inherited form of the usually sporadic myelodysplastic syndrome (MDS).[10,11] It does not have non-hematologic findings and may be caused by many of the genes listed in the table below (not an all inclusive list). 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.**

Syndrome Name	Hematologic & malignancy risks	Other features	Diagnosis	Inheritance
Congenital amegakaryocytic thrombocytopenia (CAMT)[12,13]	Isolated thrombocytopenia due to ineffective megakaryocytopoiesis at birth, with elevated plasma TPO levels. Progression to pancytopenia/aplastic 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.	N/A	Identification of mutations in MPL.	AR

Syndrome Name	Hematologic & malignancy risks	Other features	Diagnosis	Inheritance
Diamond-Blackfan anemia (DBA)[14,15]	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.	Congenital malformations in up to 50% of individuals with DBA including upper limb and hand 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 No evidence of another acquired or inherited disorder of bone marrow function DBA is caused by a mutation in one of the following genes: GATA1, RPL5, RPL9, RPL11, RPL15, RPL18, RPL26, RPL27, RPL31, RPL35, RPL35A, RPS7, RPS10, RPS15A, RPS17, RPS19, RPS24, RPS26, RPS27, RPS28, RPS29, TSR2. In up to 20% of affected individuals, the molecular cause is unknown.	Usually AD GATA1- and TSR2-related DBA are XL

Syndrome Name	Hematologic & malignancy risks	Other features	Diagnosis	Inheritance
Dyskeratosis Congenita and Related Telomere Biology Disorders (DC/TBD) [9,16-19]	At increased risk for BMF, MDS, AML, and solid tumors.	Classic DC: Classic triad of nail dysplasia, lacy reticular pigmentation of the upper chest/and or back, and oral leukoplakia. Phenotypic spectrum of TBD is broad and can also include: IUGR, cerebellar hypoplasia, immunodeficiency, retinopathy, eye abnormalities, dental abnormalities, developmental delay, short stature, microcephaly, gastrointestinal features such as liver fibrosis and genitourinary anomalies. Pulmonary fibrosis is the most common presentation of a telomere biology disorder and may be the only symptom in adults.	Identification of a mutation or mutations in one of the following genes: ACD, CTC1, DKC1, NAF1, NHP2, NOP10, PARN, POT1, RPA1, RTEL1, STN1, TERC, TERT, TINF2, WRAP53, and ZCCHC8. Approximately 70% of individuals with a clinical diagnosis are found to have a mutation in an associated gene.	AD, AR, and XL.

Syndrome Name	Hematologic & malignancy risks	Other features	Diagnosis	Inheritance
Fanconi Anemia (FA)[7,20]	At increased risk for progressive BMF with pancytopenia, usually in first decade, often initially with thrombocytopenia or leukopenia, increased risk for AML, MDS, and solid tumors (particularly of the head and neck, skin and genitourinary tract). Carriers of a subset of FA-related genes (e.g., BRCA2, PALB2, and BRIP1) have an increased risk for breast and other cancers.	Physical features are present in ~75% of individuals. These include: short stature, abnormal skin pigmentation, skeletal malformations of the upper and/or lower limbs (especially thumbs), microcephaly, ophthalmic anomalies, genitourinary tract anomalies, gastrointestinal anomalies (such as tracheoesophageal fistula), heart anomalies, otology anomalies and facial features (such as triangular face micrognathia, mid-face hypoplasia).	Increased chromosome breakage and radial forms on cytogenetic testing of lymphocytes with diepoxybutane (DEB) and mitomycin C (MMC) and/or molecular diagnosis. Fanconi Anemia is caused by a mutation or mutations in one of the following genes: BRCA1 (FANCS), BRCA2 (FANCD1), BRIP1 (FANCJ), ERCC4 (FANCQ) FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG (XRCC9), FANCI, FANCL, FANCM, PALB2 (FANCN), RAD51 (FANCR), RAD51C (FANCO), REV7 (MAD2L2/FANCV), RFWD3 (FANCW), SLX4 (FANCP), UBE2T (FANCT), XRCC2 (FANCU).	Usually AR AD (RAD51 gene) and XL (FANCB gene) cases have been reported.

Syndrome Name	Hematologic & malignancy risks	Other features	Diagnosis	Inheritance
GATA2 deficiency[21-23]	Cytopenias, myelodysplasia. Individuals have an increased risk to develop MDS and leukemias (AML and CMML). Bone marrow is typically hypocellular with characteristic features including atypical megakaryocytes, ranging from large abnormal forms with separated nuclear lobes (osteoclast-like), to smaller forms with separated nuclear lobes, micromegakaryocytes, to small hypolobated or mononuclear megakaryocytes. The majority of cases in the pediatric population who develop MDS will have monosomy 7 on bone marrow karyotype.	Viral and bacterial infections, pulmonary alveolar proteinosis and lymphedema.	Identification of a mutation in GATA2. "GATA2 mutations have been found in up to 10% of those with congenital neutropenia and/or aplastic anemia."	AD

Syndrome Name	Hematologic & malignancy risks	Other features	Diagnosis	Inheritance
SAMD9L ataxia-pancytopenia syndrome (ATXPC) and MIRAGE syndrome [24-26]	SAMD9L: variable hematologic cytopenias, and predisposition to marrow failure, myelodysplasia, and myeloid leukemia, sometimes associated with monosomy 7. SAMD9: Myelodysplastic syndrome and/or acute myelogenous leukemia (AML) with monosomy 7. Monosomy 7 may be transient if the clone is small, or it may persist for years before transformation to AML. These syndromes are likely underdiagnosed due to a common occurrence of genetic reversion to restore hematopoiesis.	SAMD9L: cerebellar ataxia SAMD9: MIRAGE (myelodyplasia, infection, restriction of growth, adrenal hyperplasia, genital phenotypes, and enteropathy) syndrome. Moderate-to-severe developmental delay is reported in most affected individuals. Autonomic dysfunction and renal dysfunction are also reported.	Identification of a mutation in SAMD9L or SAMD9.	AD
Severe congenital neutropenia (SCN) [1,27,28]	A "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." At increased risk of MDS and AML.	Severe/recurrent infections, abscesses, omphalitis, oropharyngeal inflammation, cervical adenopathy, and osteopenia. With G6PC3 mutation, developmental anomalies of the cardiac and genitourinary systems are possible.	Identification of a mutation or mutations in one of the following genes: HAX1, ELANE, AK2, GF11, CSF3R, WAS, G6PC3.	AD, AR, and XL.

Syndrome Name	Hematologic & malignancy risks	Other features	Diagnosis	Inheritance
Shwachman-diamond syndrome (SDS)[29-31]	Single or multi-lineage cytopenias. At increased risk for MDS and AML.	Exocrine pancreatic dysfunction with gastrointestinal malabsorption, malnutrition and growth failure.	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.	Usually AR. Some AD (SRP54 gene) cases have been reported.

References

Introduction

These references are cited in this guideline.

West AH, Churpek JE. Old and new tools in the clinical diagnosis of inherited bone marrow failure syndromes. *Hematololgy Am Soc Hematol Educ Program.* 2017;2017(1):79-87.

Moore, C and Krishnan K. [Updated 2020 Jul 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available at: https://www.ncbi.nlm.nih.gov/books/NBK459249/

Ghemlas I, Li H, Zlateska B, et al. Improving diagnostic precision, care and syndrome definitions using comprehensive next-generation sequencing for the inherited bone marrow failure syndromes. *J Med Genet.* 2015;52(9):575-584.

Waespe N, Dhanraj S, Wahala M, et al. The clinical impact of copy number variants in inherited bone marrow failure syndromes. *npj Genomic Med.* 2017; 2:18. doi: 10.1038/s41525-017-0019-2. PMID: 28690869; PMCID: PMC5498150.

Elghetany MT, Punia JN, Marcogliese AN. Inherited Bone Marrow Failure Syndromes: Biology and Diagnostic Clues. *Clin Lab Med*. 2021;41(3):417-431. doi:10.1016/j.cll.2021.04.014.

Pabari R, Cohen E, Cuveilier G, et al. Predictors of disease progression and survival in patients with myelodysplastic syndrome secondary to inherited bone marrow failure syndromes. *Blood.* 2019;134(Supplement 1): 2507. Available at: https://doi.org/10.1182/blood-2019-130129.

Fanconi Anemia: Clinical Care Guidelines. Fifth ed: Fanconi Anemia Research Fund; 2020.

Dror Y, Donadieu J, Koglmeier J, et al. Draft consensus guidelines for diagnosis and treatment of Shwachman-Diamond syndrome. *Ann N Y Acad Sci.* 2011;1242:40-55.

Dyskeratosis congenita and telomere biology disorders: Diagnosis and management guidelines. Second ed. New York, NY: Dyskeratosis Congenita Outreach, Inc.; 2022.

Churpek JE. Familial myelodysplastic syndrome/acute myeloid leukemia. *Best Pract Res Clin Haematol.* 2017;30(4):287-289.

Liew E, Owen C. Familial myelodysplastic syndromes: a review of the literature. *Haematologica.* 2011;96(10):1536-1542.

Geddis AE. Congenital amegakaryocytic thrombocytopenia. *Pediatr Blood Cancer.* 2011;57(2):199-203.

Dokal I, Vulliamy T. Inherited bone marrow failure syndromes. *Haematologica.* 2010;95(8):1236-1240.

Clinton C and Gazda HT. Diamond-Blackfan Anemia. 2009 Jun 25 [Updated 2021 Jun 17]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available at: https://www.ncbi.nlm.nih.gov/books/NBK7047/

Arbiv OA, Cuvelier G, Klaassen RJ, et al. Molecular analysis and genotype phenotype correlation of Diamond-Blackfan anemia. *Clin Genet.* 2018;93(2):320-328.

Savage SA, Alter BP. Dyskeratosis congenita. *Hematol Oncol Clin North Am.* 2009;23(2):215-231.

Savage SA, Niewisch MR.. Dyskeratosis Congenita and Related Telomere Biology Disorders. 2009 Nov 12 [Updated 2022 Mar 31]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available at: https://www.ncbi.nlm.nih.gov/books/NBK22301/

Glousker G, Touzot F, Revy P, Tzfati Y, Savage SA. Unraveling the pathogenesis of Hoyeraal-Hreidarsson syndrome, a complex telomere biology disorder. *Br J Haematol.* 2015;170(4):457-471.

Bertuch AA. The molecular genetics of the telomere biology disorders. *RNA Biol.* 2016;13(8):696-706.

Mehta PA and Ebens C. Fanconi Anemia. 2002 Feb 14 [Updated 2021 Jun 3]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1401/

Hsu AP, McReynolds LJ, Holland SM. GATA2 deficiency. *Curr Opin Allergey Clin Immunol.* 2015;15(1):104-109.

Hirabayashi S, Wlodarski MW, Kozyra E, Niemeyer CM. Heterogeneity of GATA2-related myeloid neoplasms. *Int. J Hematol.* 2017;106(2):175-182.

McReynolds LJ, Calvo KR, Holland SM. Germline GATA2 Mutation and Bone Marrow Failure. *Hematol Oncol Clin North Am*. 2018;32(4):713-728. doi:10.1016/j.hoc.2018.04.004.

Chen DH, Below JE, Shimamura A, et al. Ataxia-Pancytopenia Syndrome Is Caused by Missense Mutations in SAMD9L. *Am J Hum Genet.* 2016;98(6):1146-1158.

Davidsson J, Puschmann A, Tedgard U, Bryder D, Nilsson L, Cammenga J. SAMD9 and SAMD9L in inherited predisposition to ataxia, pancytopenia, and myeloid malignancies. *Leukemia.* 2018;32(5):1106-1115.

Raskind WH, Chen DH, Bird T. SAMD9L Ataxia-Pancytopenia Syndrome. 2017 Jun 1 [Updated 2021 Feb 4]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available at: https://www.ncbi.nlm.nih.gov/books/NBK435692

Klein C. Genetic defects in severe congenital neutropenia: emerging insights into life and death of human neutrophil granulocytes. *Annu Rev Immunol.* 2011;29:399-413.

Dale DC, Makaryan V. ELANE-Related Neutropenia. 2002 Jun 17 [Updated 2018 Aug 23]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1533/

Nelson AS, Myers KC. Diagnosis, Treatment, and Molecular Pathology of Shwachman-Diamond Syndrome. *Hematol Oncol Clin North Am.* 2018;32(4):687-700.

Nelson A and Myers K. Shwachman-Diamond Syndrome. 2008 Jul 17 [Updated 2018 Oct 18]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1756/