MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR FANCONI ANEMIA
POLICY NUMBER	MP 2.362

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☐ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**1/1/2025**

I. POLICY

Genetic testing for the diagnosis of Fanconi anemia may be considered **medically necessary** when the following criteria are met:

- The results of the individual's chromosome breakage test are positive; **or**
- Clinical signs and symptoms of Fanconi anemia are present; **and**
- A definitive diagnosis of Fanconi anemia cannot be made after standard workup, i.e., nondiagnostic results on chromosome breakage analysis.

Genetic testing for the diagnosis of Fanconi anemia is considered **not medically necessary** when the above criteria are not met.

Genetic testing of asymptomatic individuals to determine future risk of disease may be considered **medically necessary** when there is a first-degree relative with a documented diagnosis of Fanconi anemia.

Genetic testing for Fanconi anemia is considered **investigational** in all other situations. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

POLICY GUIDELINES

Genetic testing for Fanconi anemia (FA) is a complex process that involves multiple steps and a number of different potential approaches. Most testing procedures described in the literature involve a combination of polymerase chain reaction, direct sequencing, and next-generation sequencing to identify a full complement of variants associated with FA. *FANCA, FANCC*, and *FANCG* are the most common complement groups, but there are now twenty-three (23) known *FANC* genes (see Table 1 in Section III).

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Per the Fanconi Anemia Research Fund's Fanconi Anemia Clinical Care Guidelines, the chromosome breakage test is the first test that should be performed for an individual suspected of having FA. If the results of the chromosome breakage test are positive, genetic testing should be performed to identify the specific pathologic variant(s) associated with the individual's FA phenotype.

If the chromosome breakage test result is considered negative and the clinical evidence for FA is weak, no further studies are required. However, if there is strong clinical evidence for FA, skin fibroblast testing should be performed to rule out the possibility of somatic mosaicism. In cases where chromosome breakage testing on both blood and skin cells is negative, referral for evaluation of conditions that overlap clinically with FA should be considered.

If the chromosome breakage test results are inconclusive, further follow-up is needed. Underlying causes of inconclusive results include mosaicism in the peripheral blood cells, hypomorphic variants in *FANC* genes, and the presence of a condition other than FA that manifests with increased chromosomal breakage.

Other inherited bone marrow failure disorders can mimic FA. They include dyskeratosis congenita, Shwachman-Diamond syndrome, and congenital amegakaryocytic thrombocytopenia. Genetic testing for these other disorders is also available, targeting variants that are distinct from those seen in FA.

First-degree relatives include parents, siblings, and off-spring. Fanconi anemia can be transmitted by autosomal recessive, autosomal dominant, or X-linked inheritance. Testing the father of an individual with X-linked Fanconi anemia would not be indicated.

Carrier, preimplantation, and in utero testing for Fanconi anemia are addressed in **MP 2.258**, **MP 2.278**, and **MP 7.009**.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology— "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Diseased-Assoc.Variant	Disease-associated change in the DNA sequence.
	Variant	Change in DNA sequence

	Familial Variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives.

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely Pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association of Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Cross-reference:

MP 2.258 Carrier Screening for Genetic Diseases
MP 2.278 Invasive Prenatal (Fetal) Diagnostic Testing
MP 2.323 General Approach to Evaluating the Utility of Genetic Panels
MP 2.325 Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
MP 7.009 Preimplantation Genetic Testing

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND

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Fanconi Anemia

Fanconi Anemia (FA) is an inherited disorder that is characterized by congenital abnormalities, bone marrow failure, and predisposition to hematologic malignancies. It is rare, with an incidence of less than 10 per million live births. FA is usually transmitted by the autosomal recessive route (>99%) and by the X-linked route in a very small number of cases. The carrier frequency in the United States is approximately 1 in 300 for the general population, and as high as 1 in 100 for certain populations such as Ashkenazi Jews and South Africans of Afrikaner descent.

The clinical expression of FA is variable, but it is associated with early mortality and a high degree of morbidity. Approximately 60% to 70% have at least 1 congenital abnormality, most common being disorders of the thumb and radial bones, short stature, skin hyperpigmentation, hypogonadism, and cafe-au-lait spots. A variety of other abnormalities of internal organs such as the heart, lungs, kidneys, and gastrointestinal tract can occur in up to 20% to 25% of patients. The most serious clinical problems are bone marrow abnormalities and malignancies. Hematologic abnormalities and bone marrow failure present in the first decade of life, although they can present much later. There is an increased predisposition to malignancies, especially myelodysplastic syndrome, acute myeloid leukemia, and squamous cell cancers of the head and neck.

Diagnosis

Any patient suspected of having FA should be referred to a hematologist and/or clinical geneticist or genetic counselor, who can arrange for diagnostic testing. As FA testing is highly specialized, particularly the evaluation of chromosome breakage in response to DNA damage, only laboratories with extensive experience should undertake this testing. The chromosome breakage test is the first test that should be performed for an individual suspected of having FA. Although the chromosome breakage test is considered the gold standard for diagnosing FA, it may still produce false-negative results (the test is negative, but the patient has FA) or false-positive results (the test is positive, but the patient does not have FA).

If the results of the chromosome breakage test are positive, genetic testing should be performed to identify the specific 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.

Results may sometimes be inconclusive, leaving uncertainty as to the diagnosis of FA. In these cases, the detection of a genetic variant that is known to be pathogenic for FA can confirm the diagnosis.

Treatment

Treatment recommendations based on expert consensus were published in 2014, sponsored by the Fanconi Anemia Research Fund. For bone marrow failure, this document recommends monitoring for mild bone marrow failure and hematopoietic cell transplantation (HCT) for moderate-to-severe bone marrow failure. Androgen therapy and/or hematopoietic growth factors

are treatment options if HCT is unavailable or if the patient declines transplantation. FA patients have increased sensitivity to the conditioning regimens used for HCT and, as a result, reduced intensity regimens are used. Because of this different treatment approach, it is crucial to confirm or exclude a diagnosis of FA before HCT.

Genetics of FA

Molecular genetic testing is complicated by the presence of at least twenty-three (23) genes. For all the known genes associated with FA sequence, the analysis is complicated by the number of genes to be analyzed, a large number of possible variants in each gene, the presence of large insertions or deletions in some genes, and the size of many of the FA-related genes. If the complementation group has been established, the responsible variant can be determined by sequencing of the corresponding gene (see Table 1).

Table 1. Genes Associated with Fanconi Anemia

Gene/Complementation Group	Proportion of Individuals with Fanconi Anemia, %	Variant Type(s)
BRCA1/FANCS	<1	Sequence variants
BRCA2/FANCD1	2	Sequence variants
BRIP1/FANCJ	2	Sequence variants
ERCC4/FANCQ	<1	Sequence variants
FAAP100/FANCY	1 individual	Sequence variants
FANCA	60-70	Sequence variants; deletions/duplications
FANCB	2	Sequence variants; deletions/duplications
FANCC	14	Sequence variants; deletions/duplications
FANCD2	3	Sequence variants; deletions/duplications
FANCE	3	Sequence variants
FANCF	2	Sequence variants; deletions/duplications
FANCG (XRCC9)	10	Sequence variants
FANCI	1	Sequence variants; deletion/duplications
FANCL	<1	Sequence variants; deletions/duplications
FANCM	<1	Sequence variants; deletions/duplications
PALB2/FANCN	<1	Sequence variants; deletions/duplications
RAD51/FANCR	2 reported	Sequence variants
RAD51C/FANCO	<1	Sequence variants

REV7 (MAD2L2)/FANCV	1 reported	Sequence variants
RFWD3/FANCW	1 reported	Sequence variants
SLX4/FANCP	<1	Sequence variants; deletions/duplications
UBE2T/FANCT	<1	Sequence variants; deletions/duplications
XRCC2/FANCU	1 reported	Sequence variants

Adapted from Mehta and Ebens (2021).

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

IV. RATIONALE

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SUMMARY OF EVIDENCE

For individuals who have signs and/or symptoms of FA who receive genetic testing for FA, the evidence includes small cohort studies and case series. Relevant outcomes are test validity, other test performance measures, change in disease status, and morbid events. Due to the rarity of clinical FA, there is limited published evidence to determine whether genetic testing for FA improves outcomes. The available evidence demonstrates that most patients with a clinical diagnosis of FA have identified pathogenic variants. This supports the use of genetic testing for the diagnosis when standard testing, including chromosomal breakage analysis, is inconclusive. Therefore, when signs and/or symptoms of FA are present, but the diagnosis cannot be made by standard testing, genetic testing will improve the ability to make a definitive diagnosis and direct care. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a close relative with the diagnosis of FA who receive genetic testing for FA to determine future risk of the disease, the evidence consists of small cohort studies and case series. Relevant outcomes are test validity, other test performance measures, and changes in reproductive decision making. Genetic testing has clinical utility if there is a close relative with FA primarily first-degree relatives. This will primarily apply to young siblings of an affected individual and may help to direct early monitoring and treatment of bone marrow failure that may prevent or delay progression. Treatment of bone marrow failure with hematopoietic cell transplantation is considered more likely to be successful if initiated earlier in the course of the disease. The evidence is sufficient to determine that the technology results in an improvement in the net health outcomes.

For individuals who have a positive chromosome breakage test, societal guidance from the Fanconi Anemia Research Fund recommends genetic testing to identify the specific pathologic variant(s) associated with the patient's phenotype. Genetic testing enables accurate diagnosis, which may improve clinical care for individuals with anticipated genotype-phenotype associations as well as those who have encountered a false positive. The evidence is sufficient to determine that the technology results in an improvement in the net health outcomes.

V. DEFINITIONS TOP

NA

VI. BENEFIT VARIATIONS TOP

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER TOP

Capital Blue Cross' medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION TOP

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

Procedure Codes							
81163	81165	81212	81215	81216	81217	81242	81307
81308	81403*	81441	81479**				

*Can be used if testing for known familial variant, not otherwise specified
**Can be used for single gene testing for genes associated with Fanconi anemia (see table 1) that do not have their own code or for Fanconi anemia gene panels that may not have their own code.

ICD-10-CM Diagnosis Code	Description
D61.03	Fanconi anemia
D61.09	Other constitutional aplastic anemia
D61.89	Other specified aplastic anemias and other bone marrow failure syndromes
D61.9	Aplastic anemia, unspecified

IX. REFERENCES

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20. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 2.04.128, Genetic Testing for Fanconi Anemia. January 2024*

X. POLICY HISTORY

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MP 2.362	**05/08/2018 New Policy**. New BCBSA adoption policy. Genetic testing for Fanconi anemia may be considered medically necessary when criteria is met. Coding added.
	03/25/2019 Consensus Review. No change to policy statements, references updated.
	04/03/2020 Consensus Review. No change to policy statements. References updated. Policy variations updated to include FEP policy**.**
	02/12/2021 Minor Review. Removed Carrier Testing, Preimplantation Genetic Testing, and Fetal Testing from Policy Statement as those are discussed in other policies. Related policies added to Cross Reference section. Rationale and References updated.
	02/18/2022 Consensus Review. No changes to policy statements. FEP and references updated.
	02/17/2023 Consensus Review. Updated cross references, rationale, and references. Added 81441 to coding table.
	03/21/2024 Minor Review. Added additional indication for genetic testing. Updated policy guidelines, background, rationale, and references. Updated coding table by adding several codes for genes associated with Fanconi Anemia.

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	08/15/2024 Administrative Update. Added D61.03 as part of New Code. Eff date 10/1/2024.
	11/20/2025 Administrative Update. Removed NCCN statement.

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