



# Louisiana

## Genetic Testing for Fanconi Anemia

**Policy #** 00826

**Original Effective Date:** 05/01/2023

**Current Effective Date:** 05/01/2023

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

*Note: Invasive Prenatal (Fetal) Diagnostic Testing is addressed separately in medical policy 00690.*

### When Services Are Eligible for Coverage

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider Genetic testing of asymptomatic individuals to determine future risk of disease when there is a first-degree relative with a documented diagnosis of Fanconi anemia to be **eligible for coverage.\*\***

### When Services May Be Eligible for Coverage

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider genetic testing for the diagnosis of Fanconi anemia to be **eligible for coverage.\*\***

#### Patient Selection Criteria

Coverage eligibility for genetic testing for the diagnosis of Fanconi anemia will be considered when both of the following criteria are met:

- Clinical signs and symptoms of Fanconi anemia are present; AND
- A definitive diagnosis of Fanconi anemia cannot be made after standard workup, ie, nondiagnostic results on chromosome breakage analysis.

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# Louisiana

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## **When Services Are Considered Investigational**

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers genetic testing for Fanconi anemia in all other situations to be **investigational**.\*

The use of genetic testing for the diagnosis of Fanconi anemia when the above patient selection criteria are not met is considered to be **investigational**.\*

## **Policy Guidelines**

Genetic testing for Fanconi anemia 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 Fanconi anemia.

However, in clinical care, a more directed approach can be taken. In many cases, testing complementation groups will have been performed prior to genetic testing, and this will direct genetic testing to one of the 15 known genes associated with Fanconi anemia. Direct sequencing and/or deletion/duplication analysis of these few genes may be the most accurate and efficient approach in many cases.

In the absence of complementation testing, the greatest yield will be in testing for the *FANCA* gene, followed by the *FANCC* and *FANCG* genes. If a patient with Fanconi anemia is negative for variants in these genes, then testing for many low-frequency variants may be necessary. Next-generation sequencing offers considerable advantages in testing multiple genes simultaneously for patients in this situation.

## **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

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# Louisiana

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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	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the 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

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# Louisiana

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Policy # 00826

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American College of Medical Genetics and Genomics; AMP: Association for 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.

## **Background/Overview**

### **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 U. S. 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.

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# Louisiana

## Genetic Testing for Fanconi Anemia

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### **Diagnosis**

For patients with suspected FA after clinical and hematologic examination, the diagnosis can be confirmed by chromosome breakage analysis. A positive chromosome breakage test after exposure to alkylating agents such as diepoxybutane or mitomycin C confirms the diagnosis of FA and a negative test rules out FA. However, 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.

Other inherited bone marrow failure disorders can mimic FA. They include dyskeratosis congenita, Shwachman-Diamond syndrome, and congenital amegakaryocytic thrombocytopenia. These disorders will not typically have a positive chromosomal breakage test, but if the breakage test is not definitive, then it may be difficult to distinguish between the syndromes on clinical parameters. Genetic testing for these other disorders is also available, targeting variants that are distinct from those seen in FA.

### **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 Fanconi Anemia**

Molecular genetic testing is complicated by the presence of at least 15 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).

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# Louisiana

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Policy # 00826

Original Effective Date: 05/01/2023

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**Table 1. Genes Associated with Fanconi Anemia**

<b>Gene</b>	<b>Proportion of Individuals With Fanconi Anemia, %</b>	<b>Variant Type(s)</b>
<i>FANCA</i>	60-70	Sequence variants; deletions/duplications
<i>FANCB</i>	2	Sequence variants; deletions/duplications
<i>FANCC</i>	14	Sequence variants; deletions/duplications
<i>BRCA2</i>	3	Sequence variants
<i>FANCD2</i>	3	Sequence variants
<i>FANCE</i>	3	Sequence variants
<i>FANCF</i>	2	Sequence variants
<i>FANCG</i>	10	Sequence variants
<i>FANCI</i>	1	Sequence variants
<i>BRIP1</i>	2	Sequence variants
<i>FANCL</i>	0.2	Sequence variants
<i>FANCM</i>	0.2	Sequence variants
<i>PALB2</i>	0.7	Deletions/duplications
<i>RAD51C</i>	0.2	Sequence variants
<i>SLX4</i>	0.2	Sequence variants

Adapted from Mehta and Tolar (2013).

## **FDA or Other Governmental Regulatory Approval**

### **U.S. Food and Drug Administration (FDA)**

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# Louisiana

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Policy # 00826

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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.

### **Rationale/Source**

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Fanconi anemia is an inherited disorder characterized by congenital abnormalities, bone marrow failure, and predisposition to hematologic malignancies. The disease is associated with early mortality and a high degree of morbidity for affected individuals. The potential utility of genetic testing is in confirming the diagnosis in cases that are inconclusive after standard workup, in testing asymptomatic individuals for future risk of disease, in carrier testing for individuals at increased risk for the variant, and in the prenatal testing of a fetus that has a high-risk for the disorder.

### **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 an improvement in the net health outcomes. 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

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# Louisiana

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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.

### **Supplemental Information**

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

#### **Practice Guidelines and Position Statements**

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

#### **Fanconi Anemia Research Foundation**

In 2014, the Fanconi Anemia Research Foundation issued guidelines on diagnosis and management of the disease. The guidelines provided the following information on genetic testing:

“In the last few years, the development of next-generation sequencing (NGS) methodology, also referred to as massively parallel sequencing, has transformed the field of genetic testing because it enables detailed analysis of thousands of genes simultaneously (i.e., in parallel). Such analyses would be too time-consuming and costly to attempt using classic DNA sequencing methodologies, such as Sanger sequencing, that analyze a single gene at a time. Many laboratories have developed targeted panels of genes to be assessed by NGS to search for mutations among a group of genes that have been previously documented or have been suggested to be important in a particular disease. Such panels may include anywhere from a few genes to greater than 500. The number of genes examined varies from laboratory to laboratory depending on the testing platform and algorithm being used.”

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# Louisiana

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### **American College of Obstetricians and Gynecologists**

In 2017, the American College of Obstetricians and Gynecologists updated the committee Opinion on carrier screening for genetic diseases in individuals of Eastern European and Jewish descent. The opinion made the following 7 recommendations:

1. The family history of individuals considering pregnancy, or who are already pregnant, should determine whether either member of the couple is of Eastern European (Ashkenazi) Jewish ancestry or has a relative with one or more of the genetic conditions listed in Table 1.
2. Carrier screening for Tay-Sachs disease, Canavan disease, cystic fibrosis, and familial dysautonomia should be offered to Ashkenazi Jewish individuals before conception or during early pregnancy so that a couple has an opportunity to consider prenatal diagnostic testing options. If the woman is already pregnant, it may be necessary to screen both partners simultaneously so that the results are obtained in a timely fashion to ensure that prenatal diagnostic testing is an option.
3. Individuals of Ashkenazi Jewish descent may inquire about the availability of carrier screening for other disorders. Carrier screening is available for mucopolidosis IV, Niemann-Pick disease type A, Fanconi anemia group C, Bloom syndrome, and Gaucher disease. Patient education materials can be made available so that interested patients can make an informed decision about having additional screening tests. Some patients may benefit from genetic counseling.
4. “When only one partner is of Ashkenazi Jewish descent, that individual should be screened first. If it is determined that this individual is a carrier, the other partner should be offered screening. However, the couple should be informed that the carrier frequency and the detection rate in non-Jewish individuals are unknown for most of these disorders, except for Tay-Sachs disease and cystic fibrosis. Therefore, it is difficult to accurately predict the couple's risk of having a child with the disorder.”
5. Individuals with a positive family history of one of these disorders should be offered carrier screening for the specific disorder and may benefit from genetic counseling.
6. When both partners are carriers of one of these disorders, they should be referred for genetic counseling and offered a prenatal diagnosis. Carrier couples should be informed of the disease manifestations, the range of severity, and available treatment options. Prenatal diagnosis by DNA-based testing can be performed on cells obtained by chorionic villus sampling and amniocentesis.
7. When an individual is found to be a carrier, his or her relatives are at risk for carrying the same mutation. The patient should be encouraged to inform his or her relatives of the risk and the availability of carrier screening. The provider does not need to contact these relatives because

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# Louisiana

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there is no provider-patient relationship with the relatives, and confidentiality must be maintained.

The committee reaffirmed these recommendations in 2019.

### **U.S. Preventive Services Task Force Recommendations**

No U.S. Preventive Services Task Force recommendations for genetic testing for Fanconi anemia have been identified.

### **Medicare National Coverage**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

### **Ongoing and Unpublished Clinical Trials**

A search of [ClinicalTrials.gov](http://ClinicalTrials.gov) in November 2022 did not identify any ongoing or unpublished trials that would likely influence this review.

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# Louisiana

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Policy # 00826

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## **Policy History**

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02/02/2023 Medical Policy Committee review

02/08/2023 Medical Policy Implementation Committee approval. New policy.

Next Scheduled Review Date: 02/2024

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Policy # 00826

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### **Coding**

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81242, 81441
HCPCS	NA
ICD-10 Diagnosis	D61.09, D61.89, D61.9

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into

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Policy # 00826

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standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  1. Consultation with technology evaluation center(s);
  2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  3. Reference to federal regulations.

**\*\*Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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# Louisiana

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Policy # 00826

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**NOTICE:** If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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