Genetic Testing for 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 a rare disorder with an incidence of less than 10 per million live births. FA is usually transmitted by the autosomal recessive route 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 café-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 generally 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.

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. These include dyskeratosis congenital, 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 mutations that are distinct from those seen in FA.

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...
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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
FA is an inherited disorder, with most transmission (>99%) occurring by the autosomal recessive route, with a very small number of mutations that are X-linked. The carrier frequency is approximately 1 in 300 in the general populations and an increased carrier frequency of approximately 1 in 100 for certain populations such as Ashkenazi Jews and South African Afrikaners. Molecular genetic testing is complicated by the presence of at least 15 genes. For all the known genes associated with FA sequence, analysis is complicated by the number of genes to be analyzed, the 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 variants can be determined by sequencing of the corresponding gene.

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 (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy
Genetic testing for the diagnosis of Fanconi anemia, carrier testing (preconception and/or prenatal) for Fanconi anemia, preimplantation genetic testing for Fanconi anemia as an adjunct to in vitro fertilization, and fetal testing (in utero) for Fanconi anemia may be considered medically necessary when the below criteria are met:

Genetic testing for Fanconi anemia is considered investigational in all other situations. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application
This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Members' benefits may vary according to benefit design; therefore members benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Fanconi Anemia is covered
Genetic testing for the diagnosis of Fanconi anemia may be considered medically necessary when 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, i.e., nondiagnostic results on chromosome breakage analysis
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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 in a patient with a diagnosis of Fanconi Anemia may be considered medically necessary to identify the exact variant in an affected individual in order to benefit family members (i.e. for the purposes of genetic testing of asymptomatic individuals, carrier testing, or preimplantation/fetal testing).

Carrier testing (preconception and/or prenatal) for Fanconi anemia may be considered medically necessary when the following criteria are met:

- Previous offspring with a diagnosis of Fanconi anemia; OR
- One or both parents are known carriers of a Fanconi anemia pathogenic variant; OR
- One or both parents have a first or second-degree relative with a diagnosis of Fanconi anemia; OR
- One or both parents are members of an ethnic group with a baseline carrier frequency of 1 in 100 or greater:
  o Ashkenazi Jews
  o South Africans of Afrikaner descent

Preimplantation genetic testing for Fanconi anemia as an adjunct to in vitro fertilization may be considered medically necessary when the following conditions are met:

- Both parents are known carriers of a pathogenic Fanconi anemia pathogenic variant; OR
- One parent has a diagnosis of Fanconi anemia and the other parent is a known carrier of a pathogenic variant

Fetal testing (in utero) for Fanconi anemia may be considered medically necessary when the following conditions are met:

- Both parents are known carriers of a Fanconi anemia pathogenic variant; OR
- One parent has a diagnosis of Fanconi anemia, and the other parent is a known carrier of a Fanconi anemia pathogenic variant.

**When Genetic Testing for Fanconi Anemia is not covered**

Genetic testing for Fanconi anemia is considered [investigational](#) in all other situations not listed above as covered.

**Policy Guidelines**

The evidence for genetic testing in individuals who have signs and symptoms of Fanconi anemia includes small cohort studies and case series. Relevant outcomes are test accuracy and validity, other test performance measures, change in disease status, and morbid events. Due to the rarity of clinical Fanconi anemia, there is limited published evidence to determine whether genetic testing for Fanconi anemia improves outcomes. The available evidence demonstrates that most patients with a clinical diagnosis of Fanconi anemia have identified pathogenic variants. This supports the use of genetic testing for the diagnosis of Fanconi anemia when standard testing, including chromosomal breakage analysis, is inconclusive. Therefore, when signs and/or symptoms of Fanconi anemia 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 qualitatively that the technology results in a meaningful improvement in the net health outcome.
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The evidence for genetic testing of individuals with a close relative who has a diagnosis of Fanconi anemia to determine future risk of disease includes small cohort studies and case series. Relevant outcomes are test accuracy and validity, other test performance measures, and changes in reproductive decision making. Genetic testing has clinical utility if there is a close relative with Fanconi anemia, 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 done earlier in the course of disease. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for carrier testing of individuals who are at risk for Fanconi anemia and are considering offspring includes small cohort studies and case series. Relevant outcomes are test accuracy and validity, other test performance measures, and changes in reproductive decision making. Genetic testing is likely to have clinical utility in the reproductive setting. Fanconi anemia is a severe disorder with limited life expectancy, thus warranting consideration for carrier testing, fetal testing, and preimplantation genetic testing. In these situations, testing of selected individuals is likely to impact reproductive decisions and reduce the likelihood of having an affected offspring, therefore, health outcomes are improved. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 81242, 81479

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Specialty Matched Consultant Advisory Panel review 4/2015

Medical Director review 4/2015


Medical Director review 3/2016

Specialty Matched Consultant Advisory Panel review 3/2017

Medical Director review 3/2017
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Medical Director review 12/2017

Specialty Matched Consultant Advisory Panel review 3/2018

Medical Director review 3/2018

Policy Implementation/Update Information

5/26/15 Original Policy developed. Policy Statement: Genetic testing for the diagnosis of Fanconi anemia, carrier testing (preconception and/or prenatal) for Fanconi anemia, preimplantation genetic testing for Fanconi anemia as an adjunct to in vitro fertilization, and fetal testing (in utero) for Fanconi anemia may be considered medically necessary when the below criteria are met. Genetic testing for Fanconi anemia is considered investigational in all other situations. Medical Director review 4/2015. Specialty Matched Consultant Advisory Panel review 4/2015. Notification given 5/26/15 for effective date 7/28/15. (td)


1/12/18 Minor revisions with updated genetic nomenclature throughout policy. References updated. Medical Director review. 12/2017. (jd)


Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.