Medical Policy

Genetic Testing for Fanconi Anemia

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Policy Number: 714
BCBSA Reference Number: 2.04.128
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)
MoIDX: FANCC Genetic Testing Coding and Billing Guidelines (A53628)

Related Policies
None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

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, ie, 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.

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 mutation; 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 Afrikaaner 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 mutation; OR
- One parent has a diagnosis of Fanconi anemia and the other parent is a known carrier of a pathogenic mutation.

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 pathogenic Fanconi anemia mutation; OR
- One parent has a diagnosis of Fanconi anemia and the other parent is a known carrier of a pathogenic Fanconi anemia mutation.

Genetic testing for Fanconi anemia is considered **INVESTIGATIONAL** in all other situations.

**Medicare HMO BlueSM and Medicare PPO BlueSM Members**

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the links below.

**Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)**

**MolDX: FANCC Genetic Testing Coding and Billing Guidelines (A53628)**

For medical necessity criteria and coding guidance for Medicare Advantage members **living outside of Massachusetts**, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at [https://www.cms.gov](https://www.cms.gov).

**Prior Authorization Information**

**Inpatient**

- For services described in this policy, precertification/preauthorization is required if the procedure is performed **inpatient**.

**Outpatient**

- For services described in this policy, see below for products where prior authorization might be required if the procedure is performed **outpatient**.

<table>
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<th>Outpatient</th>
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<tr>
<td>Commercial Managed Care (HMO and POS)</td>
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<tr>
<td>Commercial PPO and Indemnity</td>
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<tr>
<td>Medicare HMO BlueSM</td>
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<td>Medicare PPO BlueSM</td>
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**CPT Codes / HCPCS Codes / ICD Codes**

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above **medical necessity criteria MUST** be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:
CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>81242</td>
<td>FANCC (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4a&gt;T)</td>
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**Description**

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.

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 mutation 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 2008, sponsored by the Fanconi Anemia Research Fund.10 For bone marrow failure, this document recommends monitoring for mild bone marrow failure and hematopoietic stem-cell transplantation (HSCT) for moderate to severe bone marrow failure. Androgen therapy and/or hematopoietic growth factors are treatment options if HSCT is unavailable or if the patient declines transplantation. FA patients have increased sensitivity to the conditioning regimens used for HSCT, 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 HSCT.

**Genetics of FA**

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 mutations 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 mutation can be determined by sequencing of the corresponding gene.
Summary
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 mutation, and in prenatal testing of a fetus that has a high risk for the disorder.

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 mutations. 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.

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 stem 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 genetic 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.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>3/2018</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>10/2016</td>
<td>Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000) clarified indicating CPT 81242 as not covered for Medicare. 10/1/2016</td>
</tr>
<tr>
<td>6/2015</td>
<td>Local Coverage Determination (LCD): Molecular Pathology Procedures (L34506) added.</td>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
References


