Policy Statement

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

- Clinical signs and symptoms of Fanconi anemia are present
- 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.

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

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

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

- Both parents are known carriers of a Fanconi anemia pathogenic variant
- 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 either of the following conditions are met:

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

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

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 (PCR), 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 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

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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.

**Coding**
The following is a specific CPT code for FANCC common variant testing:
- **81242**: FANCC (Fanconi anemia, complementation group C) (e.g., Fanconi anemia, type C) gene analysis, common variant (e.g., IVS4+4A>T)
Other testing for Fanconi anemia could be reported with the unlisted molecular pathology code 81479.

**Description**

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.

**Related Policies**

- N/A

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**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.

**Rationale**

**Background**

**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
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 FA
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).

### Table 1. Genes Associated with Fanconi Anemia

<table>
<thead>
<tr>
<th>Gene</th>
<th>Proportion of Individuals with Fanconi Anemia, %</th>
<th>Variant Type(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FANCA</td>
<td>60-70</td>
<td>Sequence variants, deletions/duplications</td>
</tr>
<tr>
<td>FANCB</td>
<td>2</td>
<td>Sequence variants, deletions/duplications</td>
</tr>
<tr>
<td>FANCC</td>
<td>14</td>
<td>Sequence variants, deletions/duplications</td>
</tr>
<tr>
<td>BRC A2</td>
<td>3</td>
<td>Sequence variants</td>
</tr>
<tr>
<td>FANCD2</td>
<td>3</td>
<td>Sequence variants</td>
</tr>
<tr>
<td>FANCE</td>
<td>3</td>
<td>Sequence variants</td>
</tr>
<tr>
<td>FANC F</td>
<td>2</td>
<td>Sequence variants</td>
</tr>
<tr>
<td>FANC G</td>
<td>10</td>
<td>Sequence variants</td>
</tr>
<tr>
<td>FANC I</td>
<td>1</td>
<td>Sequence variants</td>
</tr>
<tr>
<td>BNP1</td>
<td>2</td>
<td>Sequence variants</td>
</tr>
<tr>
<td>FANCL</td>
<td>0.2</td>
<td>Sequence variants</td>
</tr>
</tbody>
</table>
### Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

### Genetic testing for Fanconi anemia

#### Clinical Context and Test Purpose

The purpose of genetic testing for FA in patients who are symptomatic for FA, have a close relative with a confirmed diagnosis, or are at risk and are planning to start a family is to diagnose FA and direct care, including direct early monitoring and treatment of bone marrow failure or inform reproductive planning decisions.

The question addressed in this evidence review is: Does genetic testing for FA improve the net health outcome compared with standard clinical workup without testing or no testing at all in those who are symptomatic or at risk for FA?

The following PICOTS were used to select literature to inform this review.

#### Patients

The relevant populations of interest are individuals who are symptomatic for FA, those who have a close relative with a confirmed diagnosis, and those at risk who are planning a family.

#### Interventions

The relevant intervention of interest is testing for FA.

#### Comparators

The following tests and practices are currently being used to manage FA: standard clinical workup without genetic testing or no testing.

#### Outcomes

The primary outcomes of interest are bone marrow abnormalities (e.g., bone marrow failure and malignancies) and early mortality.

#### Timing

The development of bone marrow failure occurs over many years or decades with patients typically manifesting bone marrow failure by age 40.

#### Setting

Symptomatic and asymptomatic patients may be evaluated in a medical, genetics clinic for suspected Fanconi anemia.

### Table: Proportion of Individuals with Fanconi Anemia

<table>
<thead>
<tr>
<th>Gene</th>
<th>Proportion of Individuals with Fanconi Anemia, %</th>
<th>Variant Type(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FANCM</td>
<td>0.2</td>
<td>Sequence variants</td>
</tr>
<tr>
<td>PALB2</td>
<td>0.7</td>
<td>Deletions/duplications</td>
</tr>
<tr>
<td>RAD51C</td>
<td>0.2</td>
<td>Sequence variants</td>
</tr>
<tr>
<td>SLX4</td>
<td>0.2</td>
<td>Sequence variants</td>
</tr>
</tbody>
</table>

Adapted from Mehta and Tolar (2013).
**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

There is limited published data on the clinical validity of genetic testing for FA. The evidence reviewed derives from some of the larger cohorts of FA patients described in the literature, with emphasis on more recent publications, because earlier publications may not reflect the current spectrum of variants currently known.

The International Fanconi Anemia Registry is a registry of FA patients that has been maintained since 1982 at Rockefeller University. Several publications from this registry provide information on clinical validity. However, these publications tend to be variant-specific, thereby providing information on clinical validity for a specific variant. For example, Levran et al (2005) published an analysis of the spectrum of FANCA variants in patients enrolled in the International Fanconi Anemia Registry. They reported the detection rate for FANCA variants (clinical sensitivity) in 181 patients in the registry was 55%. A similar study (2003) analyzing the FANCG gene reported that pathogenic variants were identified in 9%.

De Rocco et al (2014) published the results of variant analysis of 100 unrelated patients with FA, most of whom were of Italian ancestry. All patients had a clinical diagnosis of FA and approximately half (48/100) had complementation group analysis to direct candidate gene selection, an algorithm of genetic testing that used a combination of direct sequencing, multiplex ligation-dependent probe amplification, and next-generation sequencing. A total of 108 variants were identified that were potentially pathogenic, with all patients having at least 1 variant identified and some patients having more than one. The most common involved genes were FANCA (79%), FANCG (8%), FANCC (3%), FANCD2 (2%), and FANCB (1%). Of the 108 variants, 62 had been previously identified as associated with FA, and the remaining 46 were novel variants. For the novel variants, large deletions or duplications were considered to be pathogenic, but point mutations could not always be determined as definitely pathogenic. For example, of the 85 variants in the FANCA gene, 22% were point mutations that were classified as variants of uncertain significance.

In a cohort of 80 patients from The Netherlands who were referred for genetic testing after a confirmed diagnosis of FA, Ameziane et al (2008) identified a variant in 73 (91%) patients. All patients had a comprehensive variant analysis that consisted of polymerase chain reaction, multiplex ligation-dependent probe amplification, and next-generation sequencing. Ninety-two distinct variants were detected in 73 patients, 56 of which were novel. Variants were most common in the FANCA (63%), FANCC (10%), and FANCG (7%) genes.

**Clinically Useful**
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.
No studies were identified that directly evaluated the clinical usefulness of the test.

**Chain of Evidence**
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

**Testing in Individuals with Signs and Systems of Fanconi Anemia**
The diagnosis of FA can usually be made by clinical presentation and chromosome breakage analysis. In these cases, genetic testing is not required to confirm the diagnosis. In a minority of cases, the chromosome breakage analysis is not conclusive, and the diagnosis cannot be made with certainty. In those situations, genetic testing can confirm the diagnosis of FA if a known pathologic variant is found. Genetic testing can also distinguish FA from related causes of bone marrow failure, in which variants distinct from those associated with FA are found.

**Testing in Individuals with a Close Relative with Fanconi Anemia**
Early identification of asymptomatic patients may improve outcomes by instituting treatment of early bone marrow failure that may delay or prevent the progression to complete failure. Outcomes of hematopoietic cell transplantation are likely to be optimal when patients have bone marrow failure, but do not have severe, debilitating disease and have not yet developed complications of the severe disease (e.g., opportunistic infections). Therefore, testing of asymptomatic individuals who have a first-degree relative with a diagnosis of FA is likely to result in improved outcomes.

**Testing in Individuals at Risk for Fanconi Anemia Considering Offspring**
The goal of reproductive testing is to reduce the likelihood of having an affected offspring. According to the principles outlined in the following evidence reviews, genetic testing for FA has potential clinical utility in the reproductive setting under the conditions listed.

**Carrier Testing (see Blue Shield of California Medical Policy Carrier Screening for Genetic Diseases).**
FA meets the general characteristics of a disease that warrants genetic testing. It is a disorder in which the natural history is well understood, and that has a reduced life expectancy and high morbidity. There are no other ways to diagnose the carrier state besides genetic testing. Genetic testing has an adequate sensitivity and specificity for FA, and there is a known association between the genetic variants and clinical disease. As a result, genetic testing for FA meets has potential clinical utility if the following conditions are also met:
- Previous offspring with a diagnosis of FA; OR
- One or both parents are known carriers of an FA variant; OR
- One or both parents have a first- or second-degree relative with a diagnosis of FA; OR
- One or both parents are members of an ethnic group with a baseline carrier frequency of 1 in 100 or greater:
  - Ashkenazi Jews
  - South Africans of Afrikaner descent.

**Fetal Testing In Utero (see Blue Shield of California Medical Policy: Invasive Prenatal (Fetal) Diagnostic Testing)**
Similar to the case of carrier testing, FA meets the characteristics of a disease that warrants genetic testing. As a result, fetal testing has potential clinical utility if the following conditions are also met:
- Both parents are known carriers of a pathogenic FA variant; OR
- One parent has a diagnosis of FA, and the other parent is a known carrier of a pathogenic variant.
Preimplantation Genetic Testing (see Blue Shield of California Medical Policy Preimplantation Genetic Testing).

Similar to the case of carrier testing, FA meets the characteristics of a disease that warrants genetic testing. As a result, fetal testing meets has potential clinical utility if the following conditions are also met:

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

Summary of Evidence

For individuals who have signs and/or symptoms of Fanconi anemia who receive genetic testing for Fanconi anemia, the evidence includes small cohort studies and case series. The relevant outcomes are test 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 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 that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a close relative with the diagnosis of Fanconi anemia who receive genetic testing for Fanconi anemia to determine future risk of the disease, the evidence consists of small cohort studies and case series. The 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 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 initiated earlier in the course of the disease. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are at risk for Fanconi anemia and considering offspring who receive carrier testing for Fanconi anemia, the evidence consists of small cohort studies and case series. The relevant outcomes are test 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 that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

Fanconi Anemia Research Foundation

The Fanconi Anemia Research Foundation (2014) 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.”

**American College of Obstetricians and Gynecologists**
The American College of Obstetricians and Gynecologists (2017) updated a Committee Opinion on carrier screening for genetic diseases in individuals of Eastern European and Jewish descent. The opinion made the following seven recommendations:
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. 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.

Individuals of Ashkenazi Jewish descent may inquire about the availability of carrier screening for other disorders. Carrier screening is available for mucolipidosis 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. “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.”

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.

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.

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

**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 in November 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

References


Documentation for Clinical Review

Please provide the following documentation (if/when requested):
- History and physical and/or consultation notes including:
Genetic Testing for Fanconi Anemia

2.04.128

Page 11 of 12

- Activity and functional limitations
- Clinical findings (i.e., pertinent symptoms and duration)
- Comorbidities
- Family history if applicable
- Past and present diagnostic testing and results
- Pertinent past procedural and surgical history
- Prior conservative treatments, duration, and response
- Reason for procedure/test/device, when applicable
- Treatment plan (i.e., surgical intervention)
- Consultation and medical clearance report(s), when applicable
- Radiology report(s) and interpretation (i.e., MRI, CT, discogram)
- Laboratory results
- Other pertinent multidisciplinary notes/reports: (e.g., psychological or psychiatric evaluation, physical therapy, multidisciplinary pain management) when applicable

Post Service
- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td><strong>CPT</strong></td>
<td>81242</td>
<td>FANCC (Fanconi anemia, complementation group C) (e.g., Fanconi anemia, type C) gene analysis, common variant (e.g., IVS4+4A&gt;T)</td>
</tr>
<tr>
<td></td>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
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<tr>
<td><strong>HCPCS</strong></td>
<td>None</td>
<td>None</td>
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<tr>
<td><strong>ICD-10</strong> Procedure</td>
<td>None</td>
<td>None</td>
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</table>

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>04/01/2016</td>
<td>BC BSA Medical Policy adoption</td>
<td>Medical Policy Review</td>
</tr>
<tr>
<td>06/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Review</td>
</tr>
<tr>
<td>02/01/2018</td>
<td>Policy revision without position change</td>
<td>Medical Policy Review</td>
</tr>
<tr>
<td>02/01/2019</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>
Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state government is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.