



FEP Medical Policy Manual

FEP 2.04.128 Genetic Testing for Fanconi Anemia

Effective Policy Date: April 1, 2021

Related Policies:

None

Original Policy Date: March 2019

Genetic Testing for Fanconi Anemia

Description

Fanconi anemia (FA) 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.

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing for Fanconi anemia improves the net health outcome compared with standard clinical workup or no genetic testing in individuals who are symptomatic for Fanconi anemia. This policy does not address those who have a close relative with a confirmed diagnosis, or are at risk and are planning to start a family.

POLICY STATEMENT

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.

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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 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

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

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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.

BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA 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

Summary of Evidence

For individuals who have signs and/or symptoms of Fanconi Anemia (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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Fanconi Anemia Research Foundation

In 2014, the Fanconi Anemia Research Foundation issued guidelines on diagnosis and management of the disease.¹⁵ 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

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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.”

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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
March 2019	New policy	Policy created with literature review through October 16, 2018. Genetic testing is medically necessary for the diagnosis of Fanconi anemia
March 2020	Replace policy	Policy updated with literature review through October 14, 2019. Policy statements unchanged.
March 2021	Replace policy	Policy updated with literature review through October 14, 2020; no references added. Policy statements unchanged.

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