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Corporate Medical Policy

Genetic Testing for Fanconi Anemia AHS – M2077

File Name:	genetic_testing_for_fanconi_anemia
Origination:	01/01/2019
Last CAP Review:	03/2021
Next CAP Review:	03/2022
Last Review:	03/2021

Description of Procedure or Service

Description
Fanconi anemia (FA) is an inherited disorder in which cells cannot correctly repair inter-strand crosslinks (ICLs), a specific type of DNA damage that results in genomic instability. This can lead to bone marrow failure (such as aplastic anemia), leukemia, and/or solid tumors. FA is rare, occurring in 1 in 100,000 to 250,000 births, with an increased incidence in populations such as Ashkenazi Jews and South African Afrikaner populations (Olson, 2020).

Related Policies
General Genetic Testing, Germline Mutations AHS – M2145

******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

BCBSNC will provide coverage for genetic testing for Fanconi anemia when it is determined the medical criteria or reimbursement guidelines below are met.

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. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Fanconi Anemia is covered

1. Reimbursement is allowed for genetic counseling at the time of diagnosis of Fanconi Anemia and at various points throughout a patient's life.

2. Genetic testing for the diagnosis of Fanconi Anemia is considered medically necessary when any of the following criteria are met:

   A. Clinical signs and symptoms of Fanconi Anemia are present; OR
   B. A definitive diagnosis of Fanconi Anemia cannot be made after standard workup, i.e., non-diagnostic results on chromosome breakage analysis, OR
   C. Diagnostic results on chromosome breakage test is positive

3. Prenatal/carrier testing for Fanconi Anemia is considered medically necessary when any of the following criteria are met:

A. The individual is of Ashkenazi Jewish descent; OR
B. Previous offspring with a diagnosis of Fanconi Anemia; OR
C. One parent is a known carrier of a Fanconi Anemia mutation; OR
D. One or both parents have a first or second-degree relative with a diagnosis of Fanconi Anemia.

4. Preimplantation genetic testing for Fanconi Anemia is considered medically necessary when either of the following conditions is met:

A. Both parents are known carriers of a pathogenic Fanconi Anemia mutation; OR
B. One parent has a diagnosis of Fanconi Anemia and the other parent is a known carrier of a pathogenic mutation.

When Genetic Testing for Fanconi Anemia is not covered

Genetic testing for Fanconi Anemia is considered investigational in all other conditions.

Policy Guidelines

Background

Primarily inherited as an autosomal recessive disorder, Fanconi anemia (FA) is associated with known mutations in at least 22 FA identified genes (Jung et al., 2020). It is found equally in males and females, as well as in different ethnic groups; approximately 50% of FA patients are diagnosed by age 10 (NORD, 2017). Jung et al. (2020) also noted that siblings with FA often have similar hematological courses, potentially attributed to similarity in causative variants and environmental factors but have different presentations of congenital anomalies (except for kidney abnormalities and microcephaly to a moderate degree). The three most commonly mutated genes in FA are *FANCA*, *FANCC*, and *FANCG*; these comprise up to 80-90% of all FA cases, with *FANCA* mutations accounting for approximately 60% of cases worldwide (Bogliolo et al., 2019; Olson, 2020). The main function of this set of proteins is to repair the inter-strand crosslinks (ICL) that typically form during DNA replication and transcription (Olson, 2020). A cell is estimated to repair about 10 ICLs per day, but as few as 20-40 unresolved ICLs can lead to cell death (Sumpter & Levine, 2017). The FA pathway may also play a role in other functions, such as metabolizing alcohol, ensuring the stability of the replication fork during DNA replication, managing oxidative stress as in providing defense from reactive oxygen species (ROS)-induced cell death, and repairing double strand breaks (Kottemann & Smogorzewska, 2013; Longerich, Li, Xiong, Sung, & Kupfer, 2014; Milletti et al., 2020; Olson, 2020). For example, a mutation in the *FANCC* gene was found to impede the cell's ability to clear out damaged mitochondria and viruses, which could eventually lower immunity to viral infection and contribute to the characteristic bone marrow failure (Cheung & Taniguchi, 2017; Sumpter et al., 2016).

FA may manifest in several ways with symptoms including short stature, skin findings such as hyper- or hypo- pigmentation and café-au-lait skin lesions, microcephaly, and abnormalities in the thumb, eye, axial skeleton, ear, renal system, or urinary tract. There is also a potential connection between FA and the VACTERL-H association (three or more of the following: vertebral anomalies, anal atresia, congenital heart disease, tracheoesophageal fistula, esophageal atresia, renal anomalies, limb anomalies, and hydrocephalus) as the percentage of FA patients also meeting the criteria for VACTERL-H was much higher than previously found (Alter & Giri, 2016). However, up to 25-40% of FA patients look physically normal (D'Andrea, 2010). At the

physiological level, the most common symptoms are bone marrow failure and cytopenias, such as pancytopenia, macrocytic anemia, or thrombocytopenia (Olson, 2020). Bone marrow failure is reportedly the most common primary symptom in FA and presents itself in 70-80% of patients by age ten (Bogliolo et al., 2019). Though the exact mechanism of premature hematopoietic stem cell (HSC) loss in FA remains unclear, it is thought to be impacted by defective DNA repair, causing increased damage and cell cycle arrest, increased levels of reactive oxygen species and inflammatory cytokines, and damage caused by reactive aldehydes in the absence of intact repair pathways (Olson, 2020). Aplastic anemia, another common FA side effect which causes the body to halt the production of red blood cells, also typically occurs early, either leading to death or to a hematopoietic stem cell transplant. Endocrine issues, such as growth hormone deficiency, abnormal glucose/insulin metabolism, dyslipidemia, pubertal delay, and hypothyroidism are also commonly associated with an FA diagnosis (about 80% of FA children and adults have at least one endocrine defect) and often lead to a worsening life quality in FA patients (Milletti et al., 2020; Shimamura & Alter, 2010).

Screening for Fanconi Anemia

The most common screening assay for Fanconi anemia is the chromosome breakage test. A DNA cross-linking agent, such as mitomycin C (MMC) or diepoxybutane (DEB), is used to induce chromosome breakage, and the cells are evaluated at their respective stages in the cell cycle. FA cells typically have more DNA damage and are forced to arrest in the G2 phase when these cells can be observed. Tests may be positive, negative, or inconclusive; a positive test typically shows about 90% of lymphocytes with increased breakage, a negative test shows no increased breakage, and an inconclusive test cannot provide any definitive answer (Hays, 2014). Normal cells have a mean baseline of <.05 breaks per cell while FA cells may range from 0.02 – 0.85 breaks per cell. DEB (the more sensitive and specific agent) typically has a mean baseline of <.10 breaks per normal cell and from 1.06 to 23.9 breaks per FA cell (Auerbach, 2015). The International Fanconi Anemia Registry (IFAR) found the mean standard error of breaks per cell of 104 FA patients to be 8.96 ± 0.448 and the mean standard error of percentage of cells with breaks to be 85.15% ± 1.99%, compared to 0.06 ± 0.004 breaks and 5.12% ± 0.28% of 224 non-FA patients (Kook et al., 1998).

Inconclusive results are typically due to one of two possibilities—one is "mosaicism," where two separate populations of lymphocytes in the blood occur, and the other is where the patient has another underlying condition causing chromosome breakage. However, a mutation analysis can corroborate a diagnosis or provide further information. This can be particularly helpful in assessing the patient's family members, such as potential carriers, asymptomatic family members, or members who may develop clinical symptoms (Hays, 2014).

More recently, researchers have utilized whole exome sequencing as a diagnostic method for FA. Historically, molecular diagnostics regarding FA have been challenging for the medical community because the disease is caused by hereditary patterns featuring point mutations and large genomic deletions in an estimated 22 genes (Rio et al., 2019). Nonetheless, the whole exome sequencing method used in this study identified 93.3% of deletions and mutated alleles when compared to a previously validated method, leading the researchers to the conclusion that whole exome sequencing is efficient enough to characterize patients with FA (Rio et al., 2019).

Clinical Utility and Validity

Due to the increased instability of an FA patient's genome, it is common to see an increased risk of cancer in patients with FA, particularly bone marrow cancers such as leukemia. A study found the observed to expected ratio of all cancers to be as high as 48 (i.e. the observed rate was 48 times higher than expected after controlling for factors such as age and sex) (Alter, 2014). The same study found the likelihood that an FA patient would develop acute myeloid leukemia (AML) to be 700 times higher than normal and the likelihood to develop any myelodysplastic syndrome (MDS) to be 6000 times higher (Alter, 2014). Underlying FA disease mechanisms may also be causing patients to develop cancers at a much earlier age than typically observed. A study focusing on 35 FA patients found that when compared to the general population, those afflicted by FA were, on average, diagnosed with head and neck squamous cell carcinoma 31 years earlier than controls (32 years for FA patients, 63 years for general population). FA mutation type may also play a factor in cancer development as another study found that FA patients with *FANCA* mutations developed cancer at a significantly older age than those with other mutations; however, mutation type did not seem to affect the overall survival rates of FA cancer patients (Steinberg-Shemer et al., 2019). Furthermore, the common risk factors, such as tobacco or alcohol consumption, were typically not a factor for the FA patients as is usually seen in the general population (Kutler et al., 2016).

Another example of how intertwined the FA proteins and pathway is with cancer is found in the *FANCD1* (Fanconi anemia complementation group D1) gene. The *FANCD1* gene, also known as *BRCA2*, is a gene whose mutations often lead to a higher risk of breast cancer. The *BRCA2* (-/-) cell reacts the same way an FA cell does when treated with the crosslinking agents and *BRCA2* co-localizes with *FANCD2* at damaged sections of DNA. The patients with heterozygous genotypes of *BRCA2* are historically more likely to have a higher risk of breast and ovarian cancer (D'Andrea, 2010).

Novel studies have further demonstrated the risk of germline mutations in FA complementation group (FANC) of the FA pathway in cancer. *FANCD2* (Fanconi anemia complementation group D2) was found to confer a malignant phenotype in esophageal squamous cell carcinoma, and cyclin-cyclin-dependent kinase (CDK) and ataxia-telangiectasia RAD3-related/ataxia-telangiectasia mutated (ATR/ATM) signaling was shown to help in depletion of FANCD2 protein expression and suppress cancer cell proliferation (Lei, Yu, Ko, Ning, & Lung, 2020). In a different study done on a Han Chinese population, Yu et al. (2020) identified that Fanconi anemia complement group F (*FANCF*), though already known to impact cell proliferation and DNA repair, can increase risk of colorectal cancer if hypomethylated. Aberrant methylation of *FANCF* was also observed in ovarian tumors, non-small-cell lung cancer, cervical cancer, and oral cancer previously in general populations (Yu et al., 2020). This conveys the markedly increased predisposition to cancer via mutations in FA and FA pathway components.

Guidelines and Recommendations

American College of Medical Genetics and Genomics (ACMG, 2018)

The guidelines for clinical genetics laboratories are specified in the 2018 (revised January 2018) edition of the ***Standards and Guidelines for Clinical Genetics Laboratories*** by the ACMG. The guidelines on FA state that:

- A cytogenetic evaluation for FA should include an induction of breakage with a crosslinking agent such as MMC or DEB (in addition to a baseline chromosome breakage).

- A well-established negative and positive control should be present and multiple cultures are recommended (if there is enough specimen available).

- At least 50 different cells (banded or unbanded) in the metaphase stage of the cell cycle should be analyzed, and the percentage of cells with aberration should reported (ACMG, 2018).

American College of Obstetricians and Gynecologists (ACOG) Committee Opinion on Carrier Screening for Genetic Conditions (ACOG, 2017)

In March 2017, ACOG issued a Committee Opinion on Carrier Screening for Genetic Conditions. ACOG recommends carrier screening and counseling before pregnancy; if results of screening are positive, ACOG recommends counseling the individual's partner and family. ACOG further stipulates that screening for any particular condition should only be performed once. Finally, ACOG suggests that Ashkenazi individuals should consider screening for Fanconi anemia due to the higher-than-average carrier rates for that specific population (ACOG, 2017). ACOG guidelines were reaffirmed in 2020.

Second Pediatric Blood and Marrow Transplant Consortium International Conference on Late Effects after Pediatric HCT (Dietz et al., 2017)

Due to recent increase in survival following a hematopoietic cell transplant (HCT), the conference recommends continued screening and follow up with a wide variety of specialists, with focus on the late side-effects of HCT. The conference emphasizes the importance of screening for cancer due to the increased cumulative risk (Dietz et al., 2017).

The National Organization for Rare Disorders (NORD, 2017)

NORD has published several recommendations for testing patients with suspected FA. These recommendations state that "FA should be suspected and tested for in any infant born with the thumb and arm abnormalities described previously. Anyone developing aplastic anemia at any age should be tested for FA, even if no other defects are present. Any patient who develops squamous cell carcinoma of the head and neck, gastrointestinal or gynecologic system at an early age with or without a history of tobacco or alcohol use, should be tested for FA. Many FA patients show no other abnormalities. It is essential to test for FA before contemplating stem cell transplantation for aplastic anemia or treatment for cancer, as standard chemotherapy and radiation protocols may prove toxic to FA patients (NORD, 2017)."

Cancer Care Ontario (CCO, 2016)

In December 2016, the CCO published recommendations for malignant hematology conditions. It is stated that patients with suspected aplastic anemia may be tested for FA via a peripheral blood chromosomal breakage analysis, such as the diepoxybutane test (DEB Test); further, all transplant candidates and siblings of FA patients with suspected aplastic anemia should be screened with this test (CCO, 2016).

Fanconi Anemia: Guidelines for Diagnosis and Management, 4th Edition (2014):

This guide was created from a conference held by the Fanconi Anemia Research Fund on April 5-6, 2013. The conference strongly recommended germ-line testing for patients either diagnosed with FA or who are suspected of having FA. As the disorder is inherited in an autosomal recessive manner, a germ-line test would help determine the medical management of a disorder as well as exclude other disorders with similar symptoms. A family history should also be collected to help provide the inheritance pattern and any other carriers (Hays, 2014).

The National Comprehensive Cancer Network (NCCN, 2020)

As FA often results in higher incidence of cancers, the NCCN has noted some observations regarding this condition. In the guideline for Esophageal and Esophagogastric Junction Cancers, the NCCN stated:

The genes involved include FA complementation groups A-E, with specifically identified mutations in FA-A (FANCA) and FA-C (FANCC).

- Affected individuals are identified by chromosome breakage, pancytopenia, and other hematologic abnormalities such as anemia, easy bruising and bleeding.
- "Increased frequency of squamous cell cancers of the esophagus or other squamous epithelium may be observed (NCCN, 2018).
- Karyotyping does not identify individuals with FA, but enhanced chromosomal breakage with mitomycin C can identify homozygotes but not heterozygotes
- Endoscopy of the esophagus may be considered as a screening strategy in individuals identified with FA (NCCN, 2020)."

United Kingdom National Multidisciplinary Guidelines (Shaw & Beasley,2016):

These recommendations were specifically made in the context of head and neck cancers. The recommendations for Fanconi anemia (FA) are as follows:

- "FA patients should receive vaccination against high-risk HPV virus.
- FA patients should have quarterly screening for head and neck squamous cell carcinoma and an aggressive biopsy policy…treatment for head and neck squamous cell carcinoma with surgery alone where possible"
- FA patients should follow up with a specialty Fanconi clinic (Shaw & Beasley, 2016).

U.S. Preventive Services Task Force (USPSTF) Recommendations

No U.S. Preventive Services Task Force recommendations for genetic testing for FA have been identified. A search for "Fanconi" on the USPSTF website turned up 0 results on September 21st, 2020.

Applicable Federal Regulations

No U.S. Food and Drug Administration-cleared genetic tests for FA were found as of 09/23/2020. Thus, the tests are offered as laboratory-developed tests. Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

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 service codes: 81242, 81412, 81479, 96040, S0265

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

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Specialty Matched Consultant Advisory Panel review 3/2020

Medical Director review 3/2020

Specialty Matched Consultant Advisory Panel review 3/2021

Medical Director review 3/2021

Policy Implementation/Update Information

1/1/2019	BCBSNC will provide coverage for genetic testing for fanconi anemia when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)
4/1/2019	Description updated. When Not Covered section revised; no change to policy intent. Policy guidelines and references updated. Medical Director review 4/2019. (jd)
10/29/19	Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed.

2/11/20	Annual review by Avalon 4th Quarter 2019 CAB. No revisions and no change to policy intent. Medical Director review 12/2019. (jd)
3/31/20	Specialty Matched Consultant Advisory Panel review 3/2020. Medical Director 3/2020. (jd)
2/9/21	Annual review by Avalon 4th Quarter 2020 CAB. Minor update to policy guidelines and references. Medical Director review 1/2021. (jd)
3/31/21	Specialty Matched Consultant Advisory Panel review 3/2021. Medical Director review 3/2021. (jd)