Genetic Testing for Fanconi Anemia

Policy Number: AHS – M2077 – Genetic Testing for Fanconi Anemia

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Policy Description

Fanconi anemia (FA) is an inherited disorder in which cells cannot correctly repair inter-strand crosslinks (ICLs), a specific type of DNA damage. This can lead to bone marrow failure (such as aplastic anemia), leukemia, and/or solid tumors. Fanconi anemia is rare, occurring in 1 in 100,000 to 250,000 births, with an increased incidence in populations such as Ashkenazi Jews and Afrikaner populations (Olson, 2017).

Related Policies

<table>
<thead>
<tr>
<th>Policy Number</th>
<th>Policy Title</th>
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<tbody>
<tr>
<td>AHS-M2145</td>
<td>General Genetic Testing, Germline Mutations</td>
</tr>
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</table>

Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request

1. Genetic counseling at the time of diagnosis of Fanconi Anemia and at various points throughout a patient’s life is considered MEDICALLY NECESSARY.

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. Genetic testing for the diagnosis of Fanconi Anemia IS CONSIDERED NOT MEDICALLY NECESSARY when above criteria are not met.

4. 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.

5. 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.

*The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient’s illness.*

6. Genetic Testing for Fanconi Anemia **IS CONSIDERED INVESTIGATIONAL** in all other situations

**Scientific Background**

Primarily inherited as an autosomal recessive disorder, Fanconi anemia (FA) is associated with known mutations in at least 17 FA identified genes. It is found equally in males and females, as well as in different ethnic groups; further, approximately 50% of FA patients are diagnosed by age 10 (NORD, 2017). 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 (Rio et al., 2019). The main function of this set of proteins is to repair the inter-strand crosslinks (ICL) that typically form during DNA replication and transcription. 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, and managing oxidative stress (Kottemann & Smogorzewska, 2013; Longerich, Li, Xiong, Sung, & Kupfer, 2014; Olson, 2017). 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 or thrombocytopenia (Olson, 2017). Bone marrow failure is reported the most common primary symptom in FA and presents itself in 70-80% of patients by age ten (Rio et al., 2019). 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 or abnormal glucose/insulin metabolism, are also commonly associated with an FA diagnosis (Shimamura & Alter, 2010).
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 will be evaluated at their respective stages in the cell cycle. FA cells will typically have more DNA damage and will be forced to stop in the G2 phase where 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 (Bogliolo 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 (Bogliolo 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 to be 700 times higher than normal and the likelihood to develop any myelodysplastic syndrome 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/FANCD1 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).

**Guidelines and Recommendations**

**American College of Medical Genetics and Genomics (ACMG) (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, 2017a)**

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, 2017b).

**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) (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) (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 (Hays, 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) (NCCN, 2018, 2019)**

As FA often results in higher incidence of cancers, the NCCN has noted some observations regarding this condition. It was stated that:

- 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 is observed
- 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, 2018, 2019)."

**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 prophylactic 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 October 14, 2019.

**State and Federal Regulations, as applicable**

No U.S. Food and Drug Administration-cleared genetic tests for FA were found as of 10/14/2019. 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.

**Applicable CPT/HCPCS Codes**

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<tr>
<th>Code Number</th>
<th>Code Description</th>
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<tr>
<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>
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<tr>
<td>81412</td>
<td>Ashkenazi Jewish associated disorders (e.g., Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomy, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1</td>
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<tr>
<td>81479</td>
<td>Unlisted molecular pathology</td>
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Procedure codes appearing in policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

**Evidence-based Scientific References**

ACMG. (2018). *STANDARDS AND GUIDELINES FOR CLINICAL GENETICS LABORATORIES.*


Policy Implementation/Update Information

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1/1/20</td>
<td>New Policy</td>
</tr>
<tr>
<td>3/1/20</td>
<td>Updated background, guidelines, and evidence-based scientific references. Updated background, guidelines, and evidence-based scientific references. Added in the verbiage concerning lack of published literature (for the old E&amp;I CC).</td>
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State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.