Genetic Testing for Fanconi Anemia AHS – M2077

**Description of Procedure or Service**

**Definitions**

Fanconi anemia (FA), is an inherited disorder in which cells cannot 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 Ashkenazi Jews and Afrikaner populations (Olson, 2017).

***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 to be medically necessary because the medical criteria and guidelines shown 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 is covered**

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. 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
Genetic Testing for Fanconi Anemia AHS – M2077

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 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, FA is associated with known mutations causing FA identified in at least 17 genes. The three most commonly mutated genes are FANCA, FANCC, and FANCG, comprising up to 80-90% of all FA cases. 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). At the physiological level, the most common symptoms are bone marrow failure and cytopenias, such as pancytopenia or thrombocytopenia (Olson, 2017). Aplastic anemia also typically occurs early, either leading to death or a hematopoietic stem cell transplant. There may also be assorted endocrine issues, such as growth hormone deficiency or abnormal glucose/insulin metabolism (Shimamura & Alter, 2010) However, up to 25-40% of FA patients look physically normal (D’Andrea, 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 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
Genetic Testing for Fanconi Anemia AHS – M2077

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 population 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).

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). FA patients may also tend to develop cancers much earlier than typically observed. A study focusing on 35 FA patients found that those FA patients were diagnosed with head and neck squamous cell carcinoma 31 years earlier than the general population (32 years for FA patients, 63 years for general). 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).

Applicable Federal Regulations

No U.S. Food and Drug Administration-cleared genetic tests for FA were found. 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.
Genetic Testing for Fanconi Anemia AHS – M2077

Guidelines and Recommendations

**American College of Medical Genetics and Genomics (ACMG, January 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 Fanconi anemia (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:**

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).

**Second Pediatric Blood and Marrow Transplant Consortium International Conference on Late Effects after Pediatric HCT (May 2016):**

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).

**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).

**NCCN (May 2018):**

As Fanconi anemia often results in higher incidence of cancers, the NCCN has noted some observations regarding this condition.

The genes involved include FA complementation groups A-E, with specifically identified mutations in FA-A and FA-C.
Genetic Testing for Fanconi Anemia AHS – M2077

Affected individuals are identified by chromosome breakage, pancytopenia, and other hematologic abnormalities.

Increased frequency of squamous cell cancers of the esophagus or other squamous epithelium may be observed (NCCN, 2018).

**United Kingdom National Multidisciplinary Guidelines (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 should be done with surgery alone when 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 November 6, 2018 (USPSTF, 2018).

**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*

<table>
<thead>
<tr>
<th>Code Number</th>
<th>PA Required</th>
<th>PA Not Required</th>
<th>Not Covered</th>
</tr>
</thead>
<tbody>
<tr>
<td>81242</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>81412</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>81479</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>96040</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>S0265</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

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**

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


Genetic Testing for Fanconi Anemia AHS – M2077


Genetic Testing for Fanconi Anemia AHS – M2077


Policy Implementation/Update Information

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/1/2019</td>
<td>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)</td>
</tr>
<tr>
<td>4/1/2019</td>
<td>Description updated. When Not Covered section revised; no change to policy intent. Policy guidelines and references updated. Medical Director review 4/2019. (jd)</td>
</tr>
</tbody>
</table>

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.