

Chapter 17: Genetic Counseling

Introduction

Good to Know

Genetic counseling is the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease ⁽¹⁾.

All individuals with Fanconi anemia (FA), as well as their families, should be encouraged to undergo genetic counseling by a certified genetic counselor who is familiar with FA.

Genetic counseling should be conducted at the time of diagnosis and at various points throughout a patient's life. A genetic counseling consultation should include discussions of the following:

- *Family history of FA*
- *The family's health and pregnancy histories*
- *The process by which FA is inherited*
- *The genetic testing process*
- *The patient's or parents' reproductive options and familial implications*
- *Making decisions and coping with FA*
- *FA-related research opportunities and support groups*

This chapter will discuss the role of family history, the strong recommendation for germline genetic testing, associations between genetic mutations and clinical features, genetic testing for unaffected family members, the risk of cancer in carriers of FA gene mutations, and reproductive issues in patients with FA.

Family History

A detailed family history should be collected for any individual who is suspected of having, or has been diagnosed with, FA. The patient's family history can be helpful in determining the inheritance pattern as well as provide clues as to the genetic basis of the disease. While obtaining the family history,

the genetic counselor should pay particular attention to any FA-related clinical features, as well as miscarriages and infertility.

In addition, a genetic counselor should conduct a detailed investigation of the patient's family history of cancer, with a special emphasis on leukemia and squamous cell carcinoma of the head and neck, in addition to cancers of the cervix, vulva, anus and other gastrointestinal malignancies, breast, ovaries, and prostate. If the patient's family history of cancer is suggestive of a hereditary breast and ovarian cancer syndrome, the family should undergo a risk assessment and be counseled about genetic testing for mutations in the *FANCN/PALB2* and *FANCD1/BRCA2* genes. Carriers of deleterious mutations in certain FA genes have an increased risk of cancer (see detailed information under "Cancer Risks for Carriers of FA Gene Mutations"). Cancer diagnoses should be verified with medical records whenever possible ⁽²⁾. Features of hereditary cancer syndromes can include the following:

- *Multiple close family members with cancer affecting multiple generations within the family*
- *Onset of cancer at an earlier age than expected*
- *Bilateral breast cancer*
- *Male breast cancer*
- *An individual with multiple cancers*
- *Cancer that occurs in the absence of environmental risk factors*

Ethnic background

Most mutations found in patients with FA occur regardless of ethnicity. However, in certain ethnic groups, some mutations, referred to as "founder" mutations, are found at an increased frequency (Table 1). Identifying if a patient is from one of these ethnic backgrounds can be an important factor in determining the most appropriate genetic testing strategy. If an individual's ethnic background is known to be associated with a particular FA mutation, targeted mutation analysis should be performed for that mutation. However, it is important to remember that individuals with ethnic backgrounds that are associated with specific FA mutations frequently have non-founder mutations. Therefore, such individuals who test negative for FA in a targeted mutation analysis should undergo panel testing (described below, under "Germline Genetic Testing"). If a patient's ethnic background is not associated with a specific mutation, next-generation sequencing and/or duplication/deletion testing should be completed.

Table 1. Examples of FA founder mutations in ethnic populations.

Ethnicity	Gene	Mutation(s)	Carrier Frequency	Reference
Ashkenazi Jewish	<i>FANCC</i>	c.456+4A>T (IVS4)	1 of every 90 individuals	(Whitney et al., 1993) ³ and (Verlander et al. 1995) ⁴
	<i>FANCD1</i>	c.6174delT	Approximately 1-2 of every 100 individuals	(Roa et al. 1996) ⁵
Brazilian	<i>FANCA</i>	c.3788_3790del	Unknown	(Castella et al. 2011) ⁶
	<i>FANCG</i>	c.1077-2A>G	Unknown	(Auerbach et al. 2003) ⁷
Dutch/Manitoba Mennonites	<i>FANCC</i>	c.67delG (322delG)	Unknown	(deVries et al. 2012) ⁸
French Acadian	<i>FANCG</i>	c.1480+1G>C	Unknown	(Auerbach et al. 2003) ⁷
Israeli (non-Ashkenazi Jewish)	<i>FANCA</i>	c.2172dupG (Moroccan) c.4275delT (Moroccan) c.2574C>G (Indian) c.890-893del (Tunisian)	Unknown	(Tamary et al. 2000) ⁹
Japanese	<i>FANCA</i>	c.2546delC c.3720_3724del	Unknown	(Yagasaki et al. 2004) ¹⁰
	<i>FANCC</i>	c.456+4A>T	Unknown	(Futaki et al 2000) ¹¹
	<i>FANCG</i>	c.307+1G>C c.1066C>T	Unknown	(Yagasaki et al. 2003) ¹²
Korean	<i>FANCA</i>	c.2546delC c.3720_3724del	Unknown	(Park et al. 2012) ¹³
	<i>FANCG</i>	c.307+1G>C c.1066C>T	Unknown	(Park et al. 2012) ¹³
Saudi	<i>FANCC</i>	c.165+1G>T	Unknown	(Hartmann et al. 2010) ¹⁴
South African	<i>FANCA</i> (Afrikaans)	c.1007-?_3066+?del (Transvaal Province)	Approximately 1 of every 80 individuals	(Rosendorff et al. 1987) ¹⁵
		c.1007-?_1626+?del (Transvaal Province)		(Tipping et al. 2001) ¹⁶
		c.3398delA (Transvaal Province)		(Tipping et al. 2001) ¹⁶
	<i>FANCG</i> (sub-Saharan Africans)	c.637_643del (sub-Saharan Africa)	1 of every 100 individuals	(Morgan et.al. 2005) ¹⁷
Spanish Gypsy	<i>FANCA</i>	c.295C>T	1 of every 70 individuals	(Callen et al. 2004) ¹⁸
Turkish	<i>FANCD2</i>	c.1948-16T>G	Unknown	(Kalb et al. 2007) ¹⁹

Good to Know

Autosomal recessive inheritance is one of several ways that disorders can be passed down through families.

- This type of inheritance involves genes located on one of the chromosomes numbered 1-22, which are called autosomes. Cells have two copies of every autosomal gene.
- If a disorder is **autosomal recessive**, it means that an individual must have two copies of a nonworking gene for the disease to develop.
- Individuals with a single copy of a nonworking gene for an autosomal recessive disorder are known as “**carriers**.” These individuals usually do not develop the disorder, but can pass a copy of the abnormal gene onto their children.
- In the general US population, the chance of being a carrier for any of the FA gene mutations is approximately 1 in 180 (Rosenberg et al. 2011)²⁰.
- Individuals with a rare autosomal recessive disease have an increased frequency of parents who descended from the same ancestor, known as consanguinity.
- When both parents are carriers of mutations in the same gene there are three possible outcomes with each pregnancy: a 25% chance the child has two working copies of the FA gene and is unaffected, a 50% chance the child has one nonworking copy of the gene and is a carrier, and a 25% chance the child has two nonworking copies of the gene, causing FA.

X-linked recessive inheritance involves genes located on the X sex chromosome. Males have one X chromosome; females have two. In FA, this type of inheritance applies only to the FANCB gene.

- If a disorder is **X-linked recessive**, it means that females must have two copies of a nonworking gene for the disease to develop, whereas males need only one.
- The recurrence risk for families with FANCB mutations is dependent on whether the mother is found to be a carrier of the mutation or whether it occurred sporadically (*de novo*).

Inheritance of FA

Fanconi anemia is predominantly inherited in an *autosomal recessive* fashion. However, a small fraction of individuals (approximately 2%) have mutations in the *FANCB* gene, which is inherited in an *X-linked recessive* manner. While the majority of FA follows the expected inheritance patterns, there are exceptions

(described later in the chapter) that when present will affect the recurrence risks for that couple. The exact frequency with which these atypical inheritance patterns occur is unknown.

Germline Genetic Testing

The goal of mutation analysis is to identify the specific gene changes that lead to FA. Genetic test results may help to determine the patient's medical management, prognosis, and reproductive risks, and may help to exclude diseases with similar signs and symptoms. For these reasons, genetic test results should be obtained as soon as possible. Historically, genetic testing involved chromosome breakage studies, followed by complementation group testing (described in *Chapter 2*) and the sequencing of single genes with further testing for gene deletions and duplications as needed ⁽²¹⁾. This process was expensive and lengthy ⁽²²⁾ and was not feasible for all families. Modern mutation analysis can include targeted mutation analysis, single gene sequencing, panel testing, whole exome sequencing, or whole genome sequencing. Mutations found by any of these sequencing methods can be used to perform other genetic tests such as carrier testing, prenatal testing, and preimplantation genetic diagnosis, and may in some cases help to guide the patient's medical care and/or enrollment in research studies.

Targeted mutation analysis

Targeted mutation analysis can be helpful in a variety of circumstances. Once a patient's mutation(s) has been identified, his or her family members can be tested for the same mutation(s), a process known as carrier testing. Targeted mutation analysis can also be used for prenatal testing of an unborn fetus and preimplantation genetic diagnosis of embryos generated through in vitro fertilizations. For an individual with FA, targeted testing may be the fastest and most cost-effective means of identifying mutations if the individual is of an ethnic background with a known founder mutation (Table 1). In addition, any mutations identified during research studies must be confirmed through targeted mutation analysis performed by a clinical laboratory that is certified, as described in *Chapter 2*.

Single gene sequencing

Historically, single gene sequencing was used following the completion of complementation group testing (described in *Chapter 2*). With the current trend towards increasing panel testing, single gene sequencing will likely become

less frequent in the future. However, single gene analysis may be useful for testing the partners of individuals with FA who are fertile and interested in preconception or prenatal testing. Individuals who are carriers of deleterious mutations in FA genes and who are planning a pregnancy with a new partner should also be offered single gene testing for that partner. Single gene sequencing may also be offered to family members of an individual with FA for whom specific mutations were never identified.

Panel testing

A panel of all of the known FA genes can be tested simultaneously for mutations using a technique known as next-generation sequencing. Therefore, the families of individuals who have a positive result on a chromosome breakage test (see *Chapter 2*) should be offered panel testing of known FA genes. At the time of this writing, the available panel tests include as many as 15 of the 16 known FA genes; the most recently identified FA gene, *FANCO/XPF/ERCC4*, is not included on panels, but will likely be added soon. Furthermore, due to patent restrictions the *FANCD1/BRCA2* gene may not be included in some panels and must be directly ordered through Myriad Genetics. If the patient's symptoms or family history are suggestive of a mutation in the *FANCD1/BRCA2* gene, targeted mutation analysis or single gene sequencing is recommended.

Panel testing for FA is more efficient for individuals or family members for whom a complementation group or mutations are not known, as it significantly decreases the turnaround time for results. Panel testing may also be able to identify mutations located in regions of genes known as introns, which are not typically sequenced in single gene sequencing tests⁽²²⁾. However, panel testing currently cannot detect large gene deletions, duplications, and insertions. These types of mutations can account for up to 31% of all FA mutations on average, depending on the gene involved. For example, the frequency of these mutations ranges from 4% (for mutations in the *FANCI* gene) to 73% (for mutations in the *FANCF* gene) [data collated from information in the Fanconi Anemia Mutation Database through Leiden Open Source Variation Database (LOVD v 2.0)]. Large deletions account for approximately 40% of the causative mutations that occur in *FANCA*, the most commonly mutated FA gene⁽²²⁾. Therefore, techniques that can detect gene deletions, duplications, and insertions, such as comparative genomic hybridization (CGH) or multiplex ligation-dependent probe amplification (MLPA), are an important part of the genetic testing process. These tests can be performed before or after panel

testing. Identifying large duplications and deletions with next-generation sequencing is currently available in some laboratories.

Whole exome sequencing and whole genome sequencing

In contrast to sequencing tests that analyze a single gene or a small group of genes simultaneously, whole exome sequencing analyzes all of the exons (regions of genes that direct cells to make proteins essential for bodily function) that are present in the human genome's approximately 23,000 genes, whereas whole genome sequencing analyzes the entire genome. Currently, whole exome and whole genome sequencing are available on a clinical and research basis, but may only be warranted in rare instances. For example, whole exome or whole genome sequencing may be warranted for an individual who has a diagnosis of FA based on a positive chromosome breakage test result, but who has no identifiable mutations based on the genetic testing methods discussed above. Whole exome and whole genome sequencing are beneficial for detecting mutations in a very large number of genes, but compared with single gene sequencing or panel testing, these methods are more costly, identify more genetic variants of unknown significance, and may create more ethical dilemmas ⁽²³⁾.

Benefits, risks, and limitations of genetic testing

Genetic testing has many benefits, risks, and limitations. As a result, the decision about whether to undergo genetic testing is a personal one. Individuals should be made aware of the possible implications of testing for themselves and family members (Table 2).

Associations Between Genetic Mutations and Clinical Features

In most cases, it is not possible to predict the clinical course of FA, which is a genetically and clinically heterogeneous disease. For example, siblings who have identical FA gene mutations often have radically different clinical signs and symptoms. Medical management for most individuals with FA should be selected according to the patient's clinical features. However, for individuals with mutations in the *FANCD1/BRCA2* and *FANCN/PALB2* genes, the identity of the patient's mutations is essential for proper cancer surveillance and medical management. For patients who have mutations in other FA genes like *FANCA*, *FANCC*, and *FANCG*, the identity of the patient's mutations may be helpful for prognostic purposes in some cases ⁽²⁴⁾ and occasionally may lead to

increased monitoring or early intervention. The identity of the patient’s genetic mutations may also indicate the need for detailed assessments of the patient’s clinical features and genetic background ⁽²⁵⁾.

Table 2. Some benefits, risks, and limitations of genetic testing.

Benefits	Risks	Limitations
Genetic testing results may give important information that might alter the patient’s medical management (e.g., an increase in the frequency of bone marrow biopsies)	Genetic testing information is a part of an individual’s medical record and may be examined by health and life insurance providers	Genetic testing results may not give information to guide medical management
Genetic testing results can be used for carrier testing, prenatal testing, and preimplantation genetic diagnosis	Genetic testing could reveal previously unknown family relationships (e.g., non-paternity)	One or both of the patient’s mutations may not be identified, or the genetic testing results may be inconclusive
Genetic testing information can be helpful to family members (e.g., the results may help to identify which family members may or may not be at increased risk for having a child with FA or developing cancer)	Genetic information could alter family dynamics (e.g., some family members may prefer not to know about the genetic testing results)	Genetic testing results do not enable exact predictions about future medical complications
Genetic testing results may relieve anxiety	Genetic testing results may create anxiety, distress, and feelings of guilt	
Genetic testing results may be used for inclusion in certain research projects or clinical trials		

FANCD1/BRCA2 mutations

A study published in 2002 reported that individuals with mutations in both copies (known as biallelic mutations) of the *BRCA2* gene had Fanconi anemia ⁽²⁶⁾. Subsequent studies found that individuals with biallelic *FANCD1/BRCA2* mutations develop spontaneous chromosomal aberration at a high rate ⁽²⁷⁾. These individuals also may develop leukemia at a much earlier age than is expected for individuals with mutations in other FA genes and they are also at risk of developing solid tumors such as medulloblastoma, astrocytoma, and Wilms’ tumor which are not commonly seen in individuals with mutations in other FA genes ^(28, 29). *FANCD1/BRCA2* testing should be considered in all patients with FA who have a medical and/or family history suggestive of *FANCD1/BRCA2* mutations, who do not have an identifiable mutation (as

assessed by next-generation sequencing), and/or who develop leukemia at or before the age of 5 years⁽³⁰⁾. If a patient has biallelic *FANCD1/BRCA2* mutations or a family history or clinical manifestations that are highly suggestive of *FANCD1/BRCA2* mutations, additional tests such as a brain MRI and kidney ultrasound should be performed immediately to rule out any evidence of tumors.

***FANCN/PALB2* mutations**

Mutations in the *FANCN/PALB2* gene are also associated with severe clinical features. Similar to individuals with mutations in *FANCD1/BRCA2*, individuals with mutations in *FANCN/PALB2* develop solid tumors and leukemia at an earlier age than individuals with mutations in other FA genes⁽³¹⁾. The cancer surveillance recommendations described above for patients with biallelic *FANCD1/BRCA2* mutations should also be considered for individuals with *FANCN/PALB2* mutations.

***FANCA* mutations**

One study reported that individuals with homozygous null mutations (a type of mutation that leads to the production of a nonfunctional protein or no protein at all) in the *FANCA* gene develop anemia at an earlier age and have a higher incidence of leukemia than individuals with *FANCA* mutations that result in an abnormal form of the protein⁽³²⁾. However, a separate analysis revealed that the age of onset of anemia and incidence of leukemia was not altered in patients with homozygous null mutations in *FANCA* or in patients who express an abnormal form of the protein⁽⁶⁾.

***FANCC* mutations**

A recent study noted that individuals with mutations in *FANCC* had an earlier age of onset of bone marrow failure compared with individuals with mutations in *FANCA* or *FANCG*. One mutation—known as c.456+4A>T (formerly known as IVS4)—in the *FANCC* gene is common to two different ethnic groups, but leads to very different clinical presentations. In the Ashkenazi Jewish population, this mutation leads to bone marrow failure at an earlier age than other patients with FA⁽³³⁾, whereas in the Japanese population, this mutation is associated with significantly milder symptoms⁽¹¹⁾. Furthermore, mutations located in a region of the gene known as exon 14 are associated with the development of blood abnormalities at an earlier age and poorer survival compared with individuals who have mutations in the region known as exon 1^(33,34). Several studies suggest that the c.67delG founder mutation

(formerly known as 322delG), which is common to the Dutch and Mennonite populations, is associated with milder symptoms, but exceptions have been observed⁽³⁵⁾. Studies in the Saudi population have shown that the founder mutation c.165+1G>T does not prevent the production of the protein encoded by the *FANCC* gene, and therefore may also be associated with a mild form of the disease⁽¹⁴⁾.

***FANCG* mutations**

The European FA Research Group reported that individuals with mutations in *FANCG* had more severe cytopenia and a higher incidence of leukemia than patients with mutations in other FA genes⁽³²⁾, but this pattern was not observed in the data set collected by the International Fanconi Anemia Registry (IFAR)⁽³³⁾. The discrepancies between the IFAR and European data may be due to differences in the percentages of individuals with mutations in either gene in the two populations, meaning that the IFAR may have more patients with *FANCA* or *FANCC* mutations and the European group may have more patients with *FANCG* mutations or visa versa. Therefore, mutation-specific risk information, which is more precise than complementation group-specific risk information, is sorely needed.

***FANCD2* mutations**

A study of 29 patients with hypomorphic mutations (a type of mutation that reduces the function or amount of protein that is produced from a gene) in the *FANCD2* gene reported that all of the patients in the study had one or more birth defects, which is remarkable because nearly one-third of all individuals with FA have no physical manifestations⁽¹⁹⁾. The study also reported that the median age of bone marrow failure in patients with hypomorphic *FANCD2* mutations was significantly lower than other individuals with FA (2.4 years compared with approximately 7 years, respectively).

Genetic Testing for Unaffected Family Members

If an individual's FA-causing mutations have been identified, his or her family members can then be tested using targeted mutation analysis to determine whether they carry a single copy of the same mutation. This process, known as carrier testing, can be difficult and sometimes impossible if the mutations of the patient with FA are unknown. In such cases, complete sequencing analysis of all the FA genes is technically possible, but it is not appropriate for routine

carrier testing because it could yield results that are difficult to interpret. For example, a negative test result might indicate that the family member does not carry a mutation; however, it might be possible that the individual has a mutation that the test was unable to detect. Therefore, individuals diagnosed with FA should undergo genetic testing prior to carrier testing any of the patient's family members.

Parents of children diagnosed with FA

All parents of children with identified FA-causing mutations should undergo carrier testing to confirm that they carry a copy of the same mutation.

Identifying the parental origin of the mutations enables other family members to have targeted mutation analysis for the appropriate familial mutation.

Although rare, it is possible that a parent of a child with FA will not carry either of the child's FA-causing mutations. Possible explanations for this include the following:

- *The egg or sperm involved in the child's conception had developed a spontaneous mutation (known as a de novo mutation)*
- *Only a fraction of the parent's reproductive cells have the mutation (known as germline mosaicism)*
- *Uniparental disomy in which both mutations are inherited from the same parent*
- *Misattributed paternity (the child was adopted or has a different birth father)*

Siblings of children diagnosed with FA

Due to the wide variability in the clinical symptoms associated with FA, all biological siblings of a child with FA should undergo chromosome breakage analysis (a test that is performed on a sample of blood cells). If the chromosome breakage assay is positive, genetic testing can be ordered to confirm the presence of the mutations found in the child who was originally diagnosed with FA; by contrast, if the chromosome breakage assay is negative, it greatly reduces the chance that the sibling has FA. However, the possibility of FA cannot be fully ruled out until chromosome breakage testing is performed on a second tissue source, such as skin fibroblasts (as reviewed in *Chapter 2*). A healthy sibling of an individual with FA has a 2 in 3 chance of being a carrier for the condition. Carrier testing for an autosomal recessive condition such as FA is a very personal decision and is associated with several benefits and risks (Table 2). Testing guidelines issued by the American Society of Human

Genetics and the American College of Medical Genetics state that carrier testing for children should be deferred until the child is of reproductive age and is capable of providing informed consent ⁽³⁶⁾.

Partners of individuals known to carry a FA mutation

Relatives of individuals with FA, who are known carriers of a FA mutation, are at risk of having a child with FA. For this reason, partners of individuals with FA mutations should be offered genetic counseling and genetic testing for the corresponding FA gene. For instance, if an individual is known to carry a mutation in the *FANCA* gene, his/her partner should be offered genetic testing of the *FANCA* gene (single gene sequencing should be performed first; if those results are negative, duplication/deletion testing should be performed). Because most individuals will not have a known family history of FA, testing should be offered regardless of family history of FA. This is done routinely at some institutions and is often covered by insurance, though coverage varies by plan and provider.

Children of individuals with FA

Although individuals with FA are often less fertile than their healthy peers, some individuals with FA are able to have biological children. The likelihood that a person with FA will have a child with FA depends on whether his or her partner is a carrier of an FA mutation or has FA. To determine the exact chance that a couple will give birth to a child with FA, the partner of an individual with FA should be offered genetic testing to determine whether he or she is a carrier of a mutation in the same gene as the individual with FA. Depending on the genetic testing results, the possible outcomes of the couple's pregnancies are as follows:

- If the partner is not a carrier of a gene mutation in the corresponding gene for FA, none of the couple's children would develop FA but all will be carriers of the condition.
- If the partner is a carrier of a mutation in the same gene as the individual with FA, there is a 50% chance with each pregnancy that the fetus would be affected by FA.
- If both partners have FA and have mutations in the same FA gene, all (100%) of their children will have FA.
- If both partners have FA but have mutations in different FA genes (assuming full sequencing was done of both genes), each of their children

will be a carrier for both FA genes (known as compound heterozygosity) but will not have FA.

Couples who are at increased risk of having a child with FA—including couples in which the partner’s carrier status is unknown—should be offered pre- or post-natal testing.

Cancer Risks for Carriers of FA Gene Mutations

Data collected by the International Fanconi Anemia Registry indicates that most carriers of mutations in FA genes do not have an increased risk of cancer. However, a few specific gene mutations are associated with an increased risk of cancer⁽³⁷⁾. For example, the FA genes *FANCD1*, *FANCN*, and *FANCI* are identical to the breast cancer susceptibility genes *BRCA2*, *PALB2*, and *BRIP1*, respectively, and certain mutations in these genes predispose individuals to developing breast cancer. Case control studies have shown that FA-causing mutations in *FANCI/BRIP1* and *FANCN/PALB2* are associated with a moderate risk of breast cancer^(38, 39), whereas FA-causing mutations in *FANCD1/BRCA2* are associated with a high risk of breast cancer. Family members of individuals with FA who have a mutation in one of these genes should be referred to a genetic counselor who specializes in cancer and can provide the appropriate risk information and management options.

Carriers of *FANCD1/BRCA2* mutations

Female and male relatives of individuals with biallelic mutations in the *FANCD1/BRCA2* gene have a significantly increased risk of developing certain cancers. Most carriers of mutations in the *FANCD1/BRCA2* gene will display features that are typical of patients with hereditary breast and ovarian cancer (discussed above, under “Family History”). However, a number of FA-associated mutations in the *FANCD1/BRCA2* gene do not appear to be associated with the same cancer risks that are typically seen in families with harmful *BRCA2* mutations⁽²⁹⁾. According to recent estimates, approximately 80% of women who inherit a harmful *BRCA2* mutation will develop breast cancer in their lifetimes, with roughly 40% developing breast cancer by age 80, and approximately 10-20% will develop ovarian cancer by age 70. In addition, men who inherit a harmful *BRCA2* mutation have an approximately 7% risk of developing breast cancer and a 20% chance of developing aggressive prostate cancer by age 80^(28, 40, 41). About 5% of men and women with *BRCA2* mutations may develop pancreatic cancer in their lifetimes⁽³⁹⁾. Carriers of *BRCA2*

mutations may also have an increased risk of melanoma ^(42, 43). Due to the increased risk of these specific cancers, the National Comprehensive Cancer Network has created guidelines that include cancer screening recommendations (Table 3 and Table 4) and surgical options ⁽⁴⁴⁾. Some individuals may be suitable candidates for enrollment in research studies to help increase the detection of cancers that currently do not have surveillance recommendations.

In addition to cancer screening, which can identify precancerous tumors or tumors that may be amenable to treatment, there are several ways to try to reduce the risks of cancer. The most commonly used risk-reducing procedures are chemoprevention as well as surgery (Table 5). Physicians should talk with carriers of *FANCD1/BRCA2* mutations about the risks and benefits of chemoprevention and surgery, and refer patients to the appropriate medical professionals.

Table 3. Cancer screening recommendations for female carriers of *BRCA2* mutations.

Female Screening		Recommendation
Breast	Self exam	Monthly beginning at age 18
	Clinical breast exam	Semi-annually beginning at age 25
	Mammogram	Annually beginning at age 25 or the age of the earliest breast cancer diagnosis in the family
	Breast MRI	Annually beginning at age 25 or the age of the earliest breast cancer diagnosis in the family
Ovarian	Pelvic exam	Every 6-12 months beginning at age 25
	Concurrent transvaginal ultrasound and CA-125 blood test	Every 6 months starting at age 30, or 5-10 years earlier than the age of the earliest onset of ovarian cancer in the family

Table 4. Cancer screening recommendations for male carriers of *BRCA2* mutations.

Male Screening		Recommendation
Prostate	Prostate-specific antigen (PSA) test	Consider annual exams beginning at age 40
Breast	Self exam	Provide training and education beginning at age 35
	Clinical breast exam	Every 6-12 months, starting at age 35
	Mammogram	Consider beginning at age 40 and repeating annually thereafter if gynecomastia (enlarged breasts) or high breast density is detected

Table 5. Cancer risk reduction recommendations for carriers of *BRCA2* mutations.

Prevention		Specifics
Breast	Chemoprevention	Consider on a case-by-case basis
	Prophylactic surgery (risk-reducing mastectomy)	Discuss the degree of protection afforded by surgery, reconstructive options, and associated risks
Ovarian	Chemoprevention	Consider oral contraceptives on a case-by-case basis
	Prophylactic surgery (risk-reducing salpingo-oophorectomy, which involves the removal of an ovary together with the fallopian tube)	Recommended for individuals between the ages of 35-40 or when childbearing is complete Discussion should include reproductive plans, menopausal symptoms, and the degree of breast and ovarian cancer protection afforded by surgery

Carriers of *FANCN/PALB2* mutations

Although patients with mutations in *FANCN/PALB2* and *FANCD1/BRCA2* have similar symptoms, carriers of *FANCN/PALB2* mutations may have a lower risk of cancer compared with carriers of *FANCD1/BRCA2* mutations. Recent studies suggest that having a single copy of a truncating mutation (a type of mutation that gives rise to a protein that is shorter than normal) in *FANCN/PALB2* increases the risk of breast cancer by approximately two- to five-fold^(39, 45). Another study reported that the risk of breast cancer for a woman with the *FANCN/PALB2* mutation known as c.1592delT, which is common in the Finnish population, is about 2 in 5 (or about 40%) if she lives to be age 70⁽⁴⁶⁾.

Truncating mutations in *FANCN/PALB2* have also been reported in patients with familial pancreatic cancer^(47,48), but estimates of the exact pancreatic cancer risks for carriers of *FANCN/PALB2* mutations have not been established. Some men with *FANCN/PALB2* mutations have developed breast cancer⁽⁴⁹⁾. Carriers of *FANCN/PALB2* mutations should be encouraged to discuss their cancer risks with their health care providers to design a screening plan, which may involve frequent clinical breast exams, mammograms, or breast MRI scans. However, at the time of this writing, there are no formal guidelines describing cancer-screening recommendations for carriers of *FANCN/PALB2* mutations.

Carriers of *FANCI/BRIP1* mutations

The first study to investigate the cancer risk of carriers of *FANCI/BRIP1* mutations analyzed a group of patients with hereditary breast cancer who did not have mutations in the *BRCA1* or *FANCD1/BRCA2* genes, and determined that truncating mutations in *FANCI/BRIP1* double the risk of breast cancer⁽³⁸⁾. In addition, some missense mutations (a type of mutation that gives rise to a protein containing an incorrect amino acid) in *FANCI/BRIP1* increase the risk for breast cancer while others do not. Carriers of mutations known to increase the risk of breast cancer should be encouraged to discuss their cancer risks with their health care providers to design a screening plan, as again no formal guidelines have been published.

A recent study reported that two frameshift mutations (a type of mutation that results from the addition or loss of DNA from a gene and usually gives rise to a non-functional protein) in *FANCI/BRIP1*, that are common in individuals of Icelandic heritage, are associated with an increased risk of ovarian cancer⁽⁵⁰⁾. Furthermore, the same study found that a frameshift mutation in *FANCI/BRIP1* that is common in individuals of Spanish heritage increased risk of breast cancer as well as ovarian cancer. Another study found evidence for a weak association between truncating mutations in *FANCI/BRIP1* and an increased risk of prostate cancer⁽⁵¹⁾.

Carriers of *FANCC* mutations

Mutations in the *FANCC* gene might increase the risk for breast cancer. One study reported that grandmothers who carried a *FANCC* mutation were 2.5 times more likely to develop breast cancer than noncarriers⁽³⁷⁾, but the molecular basis for the increased risk is not well understood and must be further investigated. Carriers of *FANCC* mutations should be informed of their potential breast cancer risk and encouraged to discuss this risk with their health

care providers. However, the evidence for an association between breast cancer and *FANCC* mutations remains weak ⁽⁵²⁾.

Carriers of *FANCO/RAD51C* mutations

A recent case report described an individual who had an FA-like syndrome and mutations in both copies of the *FANCO/RAD51C* gene ⁽⁵³⁾. Carriers of deleterious mutations in *FANCO/RAD51C* have been reported in families with hereditary breast and ovarian cancer ^(54, 55).

Carriers of *FANCP/SLX4* mutations

Mutations in the *FANCP/SLX4* gene have been identified in multiple patients with FA ^(56, 57). To assess the cancer risk for carriers of *FANCP/SLX4* mutations, individuals of German, Italian, or Spanish heritage and hereditary breast cancer of unknown genetic origin were screened for mutations in *FANCP/SLX4*. Truncating and splice-site mutations in *FANCP/SLX4*, which have been predicted to be harmful via computer simulations, were reported to be the cause of cancer in one family with hereditary breast cancer, and one family with hereditary breast and ovarian cancer out of several hundred families ^(58, 59, 60, 61, 62). Given the weak association, more research is needed to determine the risk for cancer in individuals carrying a *FANCP/SLX4* mutation.

Reproductive Issues

Individuals with FA may seek reproductive counseling for assistance with infertility and/or information on risks for their own children. Health care providers should also talk with parents of individuals with FA about their chances of having additional children with the disorder to permit informed decision-making regarding future pregnancies. Family planning options include natural pregnancy, adoption, birth control, prenatal testing, and various assisted reproductive technologies such as preimplantation genetic diagnosis (PGD).

Prenatal testing

Prenatal testing of fetal cells can be done at various times in pregnancy to determine whether a fetus has FA. Prenatal testing can also be used to determine whether the fetus has the same human leukocyte antigens (HLA) as the sibling with FA (this process, known as HLA typing, reveals whether the child will be a suitable donor of umbilical cord blood and/or bone marrow for the sibling with FA). Prenatal testing options include the following:

- **Amniocentesis**, typically performed between 15-18 weeks of pregnancy, involves inserting a needle through the abdomen to collect a sample of the amniotic fluid surrounding the baby
- **Chorionic villus sampling**, typically performed between 11-13 weeks of pregnancy, involves collecting a sample of fetal cells by a thin, flexible tube inserted through the vagina, or by a long, thin needle inserted through the abdomen

The goal of both procedures is to obtain fetal cells for genetic testing, chromosomal breakage testing, or molecular testing. All samples should be tested to determine whether they contain maternal cells, which will confound the test results. Targeted mutation analysis should be performed on the fetal DNA if the gene mutations are known, whereas chromosome breakage testing should be performed if the familial mutations are not known. Amniocentesis and chorionic villus sampling are associated with a risk of miscarriage. The exact risks will vary between centers; therefore, the procedures and associated risks should be discussed directly with the obstetrician or individual performing the procedure.

Preimplantation genetic diagnosis

Preimplantation genetic diagnosis (PGD) is a genetic screening test used to determine whether embryos produced through in vitro fertilization (IVF) have FA. It can also be used to identify embryos that are HLA matches for siblings. While PGD helps to reduce the likelihood that a family will have a child with FA and increases the chance that the child will be an HLA-match for the sibling with FA, it does not guarantee that the child will not have FA or be a match. There is always a chance (roughly 1-2%) that an error could occur during the process, resulting in a misdiagnosis⁽⁶³⁾. Therefore, prenatal testing should be performed during all pregnancies that result from embryos produced through in vitro fertilization with PGD.

Parents considering PGD should be advised of the chances of having a healthy, HLA-matched embryo. Theoretically, there is a 3 in 4 chance that an embryo will not have FA, and a 1 in 4 chance that an embryo will be an exact HLA match; thus, the odds that an embryo will be both free of FA and an HLA match is 3 in 16 (18.75%). In actuality, many couples will need multiple rounds of IVF and PGD to obtain a clinical pregnancy resulting in a liveborn baby. The chances of success are also impacted by a woman's age. On average, women younger than age 35 have a greater chance of success (approximately 35%)

with each cycle compared with women older than age 40 (who have a 10% chance of success) ⁽⁶⁴⁾. Each IVF and PGD center will have statistics on its success rates based on age and on FA gene mutations. Couples considering this procedure should be advised of the unique services and outcomes of the various PGD centers.

Parents should also be counseled on the financial, emotional, and other issues that arise during PGD ⁽⁶⁵⁾. The procedure can involve multiple doctor appointments, medical treatments, tough decisions, ethical and religious questions, and the addition of a new member to a family. The process has been described as an emotional rollercoaster with alternating high hopes and periods of despair ⁽⁶⁶⁾. Moral issues and religious beliefs may be important factors for patients' decision making ⁽⁶⁷⁾. It may be helpful for families to discuss PGD with other families who have gone through the process and can provide a realistic description of their experiences. A poignant memoir has been written on the topic by a mother of a child with FA, entitled *Saving Henry: A Mother's Journey* ⁽⁶⁸⁾.

Some of the key steps in the PGD process include the following:

- *Consult with a transplantation physician and genetic counselor*
- *Obtain the results of the mutation analysis*
- *Obtain the HLA type information of the individual with FA as well as the mother and father (if applicable)*
- *Consult with IVF center staff and affiliated PGD center staff*
- *Perform the required medical procedures to prepare the individual for PGD*
- *Perform PGD and choose suitable embryos for implantation and, if applicable, embryo preservation*
- *Perform a pregnancy test and prenatal testing*
- *Collect the umbilical cord blood cells*
- *Perform genetic testing on the umbilical cord blood and newborn baby*
- *Transplant HLA-matched umbilical cord into sibling*

Conclusion

Genetic counseling is an integral part of a comprehensive FA evaluation. Families should be referred to a genetic counselor who specializes in FA and is aware of the many difficult counseling issues that arise in this complex, rare disease. The genetic testing process is complex and continuously evolving. Identifying the genetic basis of the disease is of the utmost importance as it may influence a patient's clinical management, especially for severe cases. Identifying the FA-causing mutations also influences cancer screening, prenatal testing options, and preimplantation genetic diagnosis. However, the decision to proceed with any type of mutation analysis should be at the discretion of the patient or guardian. Genetic testing can have many benefits, risks, and limitations, and as a result, is a personal decision. The individual or guardian should be well informed of the possibility that the child's genetic testing results may impact his/her future reproductive health and ability to obtain life or disability insurance. These issues necessitate a detailed conversation with a genetic counselor who is familiar with FA, because misdiagnosis or misinterpretation of test results can have a significant impact on an individual with FA and his or her family members.

Chapter Committee

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