Clinical Management Guidelines for Friedreich Ataxia

Chapter 11. Genetic issues in Friedreich ataxia

Contents

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11. Genetic issues in Friedreich ataxia

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In this chapter, the genetic aspects of Friedreich ataxia are described, as well as genetic and other testing options for adults and minors at risk of Friedreich ataxia. The complexity of pre-symptomatic testing for minors is discussed, along with genetic counseling issues related to testing for Friedreich ataxia for family members. In making recommendations for management of testing for at-risk family members, the authors were tasked with answering the following questions:

For adult siblings of a person with Friedreich ataxia, what is the best management for testing? (see 11.2)

For minor siblings of a person with Friedreich ataxia, what is the best management for testing? (see 11.3)

For individuals with or at risk of Friedreich ataxia what is the best management for questions related to GAA repeat size? (see 11.5)

11.1 Genetics of Friedreich ataxia

As described in Chapter 1: section 1.2, Friedreich ataxia (FRDA) is an autosomal recessive condition caused by biallelic pathogenic variants in the *FXN* gene. Approximately 96% of affected individuals are homozygous for an expansion of a GAA trinucleotide repeat in intron 1 of this gene and about 4% are compound heterozygous, with a triplet repeat expansion in one allele and another pathogenic variant in the other (1). Only one family with a homozygous point mutation has been reported (2). In those homozygous for the GAA repeat expansion, there is an inverse correlation between the size of the smaller repeat (GAA1) and disease severity, including age at symptom onset (3-5).

11.2 Management of testing for adult siblings of a person with Friedreich ataxia

At the time of conception, the siblings of a person with FRDA have a 1-in-4 risk of having two *FXN* pathogenic variants and being affected by FRDA. The risk for an individual sibling, however, depends on their age. If they are younger than the proband was at the onset of symptoms, their risk of having FRDA is essentially 1 in 4. If they are older and asymptomatic the risk can be lower, since the probability of having FRDA decreases as an individual becomes older and doesn't have symptoms. However, even if the sibling is many years older than the age at which the proband developed symptoms, there still remains a risk of disease given the possibility of marked differences in age of onset within the same family. This relates largely to when siblings inherit different size expanded *FXN* GAA repeats.

11.2.2 Carrier testing for adult siblings

The goal of carrier testing for adult siblings of a person with FRDA is to allow for reproductive planning. The decision to undergo carrier testing should be voluntary and made after appropriate genetic counseling, which should include a review of the autosomal recessive inheritance pattern and natural history of FRDA. Carrier status for FRDA does not in itself confer any medical risk. It should be emphasized to the person undergoing testing that while a carrier for FRDA is healthy, they are at risk of transmitting the *FXN* pathogenic variant to offspring.

When an adult sibling requests carrier testing, a clinician should:

- inform the person that their risk of being a carrier at conception was 1 in 2, but if they are much older than their sibling was at symptom onset, the chances of being a carrier is about 2 in 3 (since the 1-in-4 chance of being affected is by then close to zero).
- warn that there is a small chance that testing will identify that they have two *FXN* pathogenic variants and will at some point develop symptoms of the condition. There should be a thorough discussion about the pros and cons of such testing.
- offer a neurological examination as this may identify subtle features of the condition such as mild ataxia, absent lower limb reflexes, altered vibration sense and/or altered proprioception.
- offer to arrange psychological support if signs of FRDA are identified. The absence of any clinical signs of FRDA means the risk of that person being diagnosed with the condition through genetic testing is low. If subtle symptoms are identified then the individual should be forewarned about the possibility that FRDA may be diagnosed and provided with appropriate psychological support.
- arrange follow-up genetic counseling to discuss testing of their current/future partner (if the sibling is heterozygous for a *FXN* pathogenic variant), risks to future pregnancies as well as options for prenatal diagnosis and preimplantation genetic testing (if that is available).

11.2.2 Other examinations for at-risk adult siblings

If siblings do not wish to undergo genetic testing, or may do so at some time in the future, other tests may be offered to ensure that if symptoms develop, they are recognized and treated. Siblings can be offered a physical examination, but they need to be informed that signs of FRDA may be found. Cardiac disease is common in FRDA and echocardiography and electrocardiogram can be offered to look for cardiac signs while the sibling can avoid a definitive diagnosis of FRDA. If no signs of FRDA are identified through physical examination or cardiac testing, this can provide reassurance to the at-risk sibling but cannot exclude the possibility of biallelic *FXN* pathogenic variants being present.

Best practice statements

Requests for carrier testing by at-risk adult siblings are best managed on a case-by-case basis; there is no evidence to support the routine provision or refusal of carrier testing for Friedreich ataxia.
All at-risk siblings identified as having Friedreich ataxia pre-symptomatically and their families would benefit from immediate post-test counseling and psychosocial support and referral for appropriate neurological and cardiac surveillance.

Recommendations

Grading for strength of recommendation and level of evidence

For the rating of the **strength** of the recommendation, in addition to evidence from studies in FRDA, evidence from like conditions, clinical experience and expert consensus are taken into account when published evidence is not available.

The **level of evidence** is based on published evidence from studies in FRDA. If there is no published evidence in FRDA, evidence from other like conditions or clinical expertise may have been used to

make the recommendation – this is graded as 'very low' or in some cases 'low' level evidence. See the table below for an explanation of the symbols used to grade recommendations.

Strength of recommendation	Symbol	Level of evidence	Symbol
Strong for intervention	↑↑	High	⊕⊕⊕⊕
Conditional for intervention	↑	Moderate	⊕⊕⊕◯
Neither intervention nor comparison	—	Low	⊕⊕◯◯
Conditional against intervention	↓	Very low	⊕◯◯◯
Strong against intervention	↓↓		

Echocardiography for at-risk adults

Should offering echocardiograms versus no echocardiograms be used for untested adult siblings of people with Friedreich ataxia?	Strength	Level of evidence
We suggest that adult siblings of a person with Friedreich ataxia, who do not wish to have genetic testing to confirm whether or not they have Friedreich ataxia, be offered echocardiography to see if they have any cardiac signs that may require treatment.	↑	⊕◯◯◯
Justification: Cardiac involvement is the main cause of mortality in Friedreich ataxia (6) and can be treated to reduce the chance of cardiac morbidity and mortality. Offering echocardiography can enable a person who does not wish to have genetic testing to avoid possible definitive diagnosis of Friedreich ataxia, while at the same time maintaining safety. Identification of cardiac abnormality by echocardiography may lead to treatment that can reduce morbidity and mortality. Normal echocardiography may result in reduced anxiety for the individual.		
Subgroup considerations: This recommendation is for untested adult siblings of individuals with Friedreich ataxia.		

Physical examination for at-risk adults

Should offering a physical examination versus no physical examination be used for adult siblings of people with Friedreich ataxia?	Strength	Level of evidence
We suggest that adult siblings of people with Friedreich ataxia should be offered a physical examination. They should be made aware that this could identify signs of Friedreich ataxia. Absence of signs of Friedreich ataxia does not mean that they will not be found to have biallelic pathogenic variants in *FXN*. The older the individual with a normal examination, the less likely they are to have biallelic pathogenic variants in *FXN*.	↑	⊕◯◯◯
Justification: Although there is no published evidence, clinical experience indicates that siblings of people with Friedreich ataxia often value the outcome of a physical examination. The key here is that it should be offered as an option and not be made mandatory. In offering the option, the possibility of identifying signs of Friedreich ataxia should be made known to the individual before the examination.		

Subgroup considerations: This recommendation is for adult siblings of individuals with Friedreich ataxia.

Lay summary

Lay summary of clinical recommendations for testing for adult siblings of a person with Friedreich ataxia

Why these recommendations?

When they are conceived, the brothers and sisters (siblings) of a person with Friedreich ataxia have a 1-in-4 chance of having two faulty *FXN* genes and therefore having Friedreich ataxia. As a sibling becomes older and does not have symptoms, the more likely it is that they *don't* have the condition.

Testing for Friedreich ataxia is different depending on whether the sibling is an adult or a child. Adult siblings who do not show symptoms of Friedreich ataxia may want to be tested for Friedreich ataxia to see if they are a carrier of the condition, particularly if they are thinking about starting a family. Testing an adult sibling who has no symptoms is unlikely to show that they have Friedreich ataxia, but occasionally it can do so.

Some adult siblings prefer not to have testing for Friedreich ataxia, but they can have other tests in case they have any symptoms that can be treated.

We suggest that adult individuals who choose not to be tested can have heart ultrasound and electrocardiogram (also called an ECG or EKG) to see if they have any symptoms that may need treatment. Offering heart screening can enable a person who does not wish to have genetic testing to avoid possibly knowing they have Friedreich ataxia, while at the same time maintaining their safety.

For those adults who request testing for Friedreich ataxia, we suggest in the first instance they are offered a physical examination to check for features of the condition.

What does this mean for you as a person living with Friedreich ataxia or caring for someone living with Friedreich ataxia?

It might be important for you to speak with your healthcare professional about testing for Friedreich ataxia and what it means for you.

Who are these recommendations specifically for?

These recommendations are specifically for adult brothers or sisters of individuals with Friedreich ataxia.

11.3 Management of testing for minor siblings of a person with Friedreich ataxia

The issues related to testing minor siblings of a person with FRDA differ depending on whether the sibling is a mature or immature minor. A mature minor is defined as a person younger than 18 years of age who has the capacity to make healthcare decisions whilst an immature minor does not. There is no specific age at which an immature minor becomes a mature minor. The process of becoming a mature minor is a gradual one. Assessment of whether a minor can make a particular healthcare decision needs to be judged on a case-by-case basis.

11.3.1 Carrier testing for minor siblings

Carrier testing of children for autosomal recessive conditions for the purpose of reproductive planning is not generally recommended (7-11). As discussed below, because of the variable age of onset of FRDA, there is always a possibility that genetic testing of the *FXN* gene will identify that the person will go on to develop FRDA (in this case it would be considered pre-symptomatic genetic testing). The basic principle which guides this general approach to carrier testing in minors is the child's right to self-determination, autonomy, and privacy, and concerns regarding a child's ability to provide voluntary informed consent to genetic testing. A systematic review of 14 guidelines/practice statements from 24 different groups concluded that carrier testing should not be performed in children, and that testing should be deferred until the child is able to provide informed consent (9). There are cases where exceptions to this general rule may be in the best interest of the minor and his or her family (12, 13), as in the case of an emancipated minor (a minor who is legally independent of their parents) or adolescent. A large survey of clinical geneticists identified cognitive, emotional and sexual maturity of the minor and parental support as crucial factors in deciding whether to disclose genetic risk to children or to allow adolescents to request carrier testing (14).

In general, carrier testing in children for FRDA for the sole purpose of reproductive planning should be deferred until the child is able to fully participate in the decision to undergo genetic testing. In the case of an emancipated minor or mature, well-informed adolescent, the decision to undergo genetic testing should always be preceded by appropriate genetic counseling with the decision to test or not being made on a case-by-case basis. The potential psychological and social risks should be discussed, particularly the potential to identify future risk of FRDA for the adolescent, and they should be encouraged to involve their parents in the decision process. There is little data to show the extent of benefits and harms associated with pre-symptomatic testing in minors, but a study of nine individuals who underwent pre-symptomatic testing for adult-onset disorders (six gene positive) did not identify adverse outcomes from knowing their genetic status (15).

11.3.2 Pre-symptomatic testing for minor siblings

Genetic testing of an at-risk individual who has no clinical symptoms of the disease is considered pre-symptomatic testing. As FRDA is characterized by a wide range in age of onset and variable intergenerational instability of the GAA expansion, a sibling of an individual with FRDA may have inherited two *FXN* pathogenic variants but not yet developed symptoms at the time of clinical evaluation. There is considerable difference of opinion within the genetics community regarding if or when to offer pre-symptomatic genetic testing for childhood or adolescent-onset disorders that do not have definitive medical therapies or preventive measures, as is the case for FRDA. A survey of 177 clinical geneticists revealed the majority was unwilling to provide a pre-symptomatic genetic test for children in this specific situation, although for adolescents they were significantly more willing to do so if the request was made together with the adolescent's parents (14).

A review of current guidelines on pre-symptomatic testing from four major genetics societies revealed general consensus and acknowledgement that each situation is unique and should be managed on a case-by-case basis (7, 8, 10, 11). All four societies maintain that the primary justification for pre-symptomatic genetic testing in children and adolescents should be timely medical benefit or substantial psychosocial benefit in the absence of definitive medical benefit. Other general recommendations include the need for detailed and careful genetic counseling for the parents and child, commensurate on maturity, prior to the initiation of any pre-symptomatic genetic testing. The genetic counseling session should include exploration of the psychological and social risks and benefits of early genetic diagnosis from both the parents' and child's perspectives. When

possible, the child should be involved in the decision-making process and documentation of their assent should take place.

There are currently no published guidelines or studies which specifically address the issue of pre-symptomatic genetic testing for FRDA. The subcommittee that produced these current guidelines did not reach consensus on the issue of pre-symptomatic testing of minors. Reasons for not offering pre-symptomatic genetic testing for FRDA included the need to respect the minor's autonomy and freedom to choose whether or not to undergo genetic testing when they reach adulthood, and the lack of effective treatments to slow progression of FRDA at this time. Reasons for offering pre-symptomatic genetic testing for FRDA included the potential benefit of surveillance for cardiac manifestations of FRDA (i.e., cardiomyopathy), the potential for the family to plan for the future needs of their child, and the potential for the affected minor to participate in clinical trials of therapeutic agents at an early stage of the disease course. There are currently no studies which specifically address early treatment of cardiac manifestations in pre-symptomatic FRDA. However, clinical screening protocols and genetic testing (with appropriate genetic counseling) for family members at risk of inherited forms of cardiomyopathy, which include FRDA, is standard of care (16, 17). Given the difficulty in reaching consensus, the subcommittee recommends a multidisciplinary approach to pre-symptomatic genetic testing in children for FRDA.

A qualitative study aimed to ascertain the opinions of individuals with FRDA (n=10) and parents (n=10) regarding pre-symptomatic testing of minors via semi-structured interview (18). Four findings emerged. First, a number of arguments for and against testing minors were identified. Second, strong support existed from parents about the parental right to test their at-risk immature children, but individuals with FRDA were of mixed opinions. Third, both individuals with FRDA and parents felt it was not the clinician's role to make the final decision about whether testing occurs. Finally, a specific issue of concern was what and when to tell at-risk children about the test result.

11.3.3 Other examinations for at-risk minor siblings

If siblings do not undergo genetic testing other tests may be offered to ensure that if symptoms develop, they are recognized and treated. Siblings can be offered a physical examination, but they need to be informed that signs of FRDA may be found. Cardiac disease is common in FRDA and echocardiography and electrocardiogram can be offered to look for cardiac signs while the sibling can avoid a definitive diagnosis of FRDA. If no signs of FRDA are identified through physical examination or cardiac testing, this can provide reassurance to the at-risk sibling and parents but cannot exclude the possibility of biallelic *FXN* pathogenic variants being present.

Recommendations

Echocardiography for at-risk minors

Should offering echocardiograms versus not offering echocardiograms be used for untested siblings (minors) of a person with Friedreich ataxia?	**Strength**	**Level of evidence**
If an asymptomatic at-risk minor sibling of a person with Friedreich ataxia has not had genetic testing to confirm whether or not they have the genetic predisposition to Friedreich ataxia, we suggest they should be offered echocardiography to assess if they have cardiac morbidity that may require treatment. The minor (when of maturity to understand) and their parents should be made aware that	↑	⊕◯◯◯

echocardiography can identify that the child has Friedreich ataxia on the basis of the presence of typical cardiac findings. They should also be made aware that a normal echocardiogram does not exclude the diagnosis of Friedreich ataxia.		
Justification: Treatment of cardiac morbidity may reduce symptoms and risk of mortality.		
Subgroup considerations: This recommendation is for untested siblings (minors) of people with Friedreich ataxia.		

Additional psychological support for at-risk minors

Should additional support services, such as psychologist, ethicist, versus no additional support services be used for minors at risk of Friedreich ataxia?	**Strength**	**Level of evidence**
We suggest minors at risk of Friedreich ataxia (siblings of people with Friedreich ataxia) should be offered psychological support to assist with dealing with anxiety that may arise from being at risk of developing the condition.	↑	⊕◯◯◯
Justification: Being at risk of Friedreich ataxia may result in considerable psychological distress for the individual.		
Subgroup considerations: This recommendation is for siblings (minors) of people with Friedreich ataxia. The need for psychological support may vary with the age of the sibling and their testing status, particularly as the sibling moves from being an immature to a mature minor. Need should be assessed on an individual basis.		

Testing for immature minors

Should offering testing versus not offering testing be used for immature minors at risk of Friedreich ataxia?	**Strength**	**Level of evidence**
We cannot recommend the routine offer of pre-symptomatic genetic testing over refusal to offer testing for immature minors at risk of Friedreich ataxia. Each situation is unique and should be managed on a case-by-case basis with referral to a team with expertise in pre-symptomatic genetic testing and the related issues.	—	⊕◯◯◯
Justification: As there is no evidence to support the routine provision or refusal of pre-symptomatic genetic testing for Friedreich ataxia to immature minors at this time, each situation should be managed on a case-by-case basis. However, clinical experience suggests the following considerations: (i) The family should be referred to a team with expertise in this field for discussion about testing. (ii) The risks and benefits of pre-symptomatic genetic diagnosis from both the child's and parents' perspectives should be carefully reviewed during the pre-test assessment. (iii) Minors who have the maturity to do so, should be involved in the decision as to whether or not they are tested. (iv) A multidisciplinary approach to the pre-symptomatic testing process, with the additional involvement of a psychologist or psychiatrist with expertise in pediatric and adolescent issues should be employed in the process.		

(v) All minors identified pre-symptomatically with the genetic predisposition to Friedreich ataxia and their families should receive immediate post-test counseling and psychosocial support. (vi) All minors identified pre-symptomatically should be referred for appropriate neurological and cardiac surveillance. If a therapy emerges that is proven to delay the onset and slow progression of Friedreich ataxia then proactive testing of unaffected siblings of individuals with Friedreich ataxia will be recommended.
Subgroup considerations: This recommendation is for immature minors at risk of Friedreich ataxia. National regulations need to be taken into account as in some jurisdictions, pre-symptomatic testing of minors is not permitted.

Testing for mature minors

Should offering testing versus not offering testing be used for mature minors at risk of Friedreich ataxia?	**Strength**	**Level of evidence**
We conditionally recommend testing over refusal of testing for an asymptomatic mature at-risk minor who requests genetic testing for Friedreich ataxia. When a mature minor requests testing, a referral should be made to a team with expertise in pre-symptomatic genetic testing for Friedreich ataxia and the related issues.	↑	⊕◯◯◯
Justification: A 'mature' minor is defined as a person younger than 18 years who is deemed to have the capacity to make healthcare decisions on their own behalf and as such can weigh up the benefits and risks of testing for themselves. However, support for the decision-making process is integral to offering testing, with the following considerations: (i) The views of the mature minor in relation to testing should be central to the decision as to whether testing takes place or not. Where the parents/guardians wish testing to take place but the mature minor does not, testing should not proceed. (ii) The mature minor +/- their parents/guardians should be referred to a team with expertise in this field for discussion about the request. (iii) The risks and benefits of pre-symptomatic genetic diagnosis from the perspectives of both the mature minor and their parents/guardians should be carefully reviewed during the pre-test assessment. (iv) A multidisciplinary approach to the pre-symptomatic testing process, with the additional involvement of a psychologist or psychiatrist with expertise in adolescent issues, should be considered. (v) All patients identified pre-symptomatically and their families should receive immediate post-test counseling and psychosocial support. (vi) All patients identified pre-symptomatically should be referred for appropriate neurological and cardiac surveillance. If the mature minor does not have biallelic *FXN* pathogenic variants then they will not develop Friedreich ataxia and this will generally result in relief of anxiety for the individual and their family, although some individuals may have a negative response to this finding due to the phenomenon of "survivor guilt". If they are found to have biallelic *FXN* pathogenic variants, this is very likely to result in anxiety for the individual and their family, but from a medical perspective there are benefits in that they can have surveillance for cardiac involvement and therapy for this can be instituted when indicated.		

Subgroup considerations: This recommendation is for mature minors at risk of Friedreich ataxia. National regulations need to be taken into account as in some jurisdictions, pre-symptomatic testing of minors is not permitted.

Lay summary

Lay summary of clinical recommendations for testing for minor siblings of a person with Friedreich ataxia

Why these recommendations?

Being unsure about whether or not they are going to develop symptoms of Friedreich ataxia may cause worry and distress for brothers and sisters (siblings) of a person with the condition. We suggest the siblings of individuals with Friedreich ataxia be offered support to help with managing any worry about the possibility of developing symptoms.

For children who are siblings of a person with Friedreich ataxia but do not have symptoms, we cannot say if having a test for Friedreich ataxia is better than not having a test, because it will be different for each person and family. It is important that the family of the person with Friedreich ataxia is referred to a multidisciplinary team (including doctors and counselors) with expertise in this situation who will be able to provide specific advice to each family. Discussion with the team should include the positive and negative aspects of testing from both the child's and parents' viewpoints. Where possible and if sufficiently mature, the child should be involved in making a decision about testing.

In the case of a request for testing for Friedreich ataxia from a "mature minor" (that is, someone who is under the age of 18 years, but is considered capable of making health-related decisions for themselves) who does not show symptoms, we suggest testing under the following conditions:

- The views of the mature minor requesting testing should be central to the decision as to whether testing takes place or not. Where the parents/guardians wish testing to take place but the mature minor does not, testing should not proceed.
- The mature minor, with or without their parents/guardians, should be referred to a multidisciplinary team (possibly including a psychologist or psychiatrist who works with adolescents) with expertise in this field for discussion about the request.
- The risks and benefits of a genetic diagnosis of Friedreich ataxia before symptoms appear (pre-symptomatic) from the perspectives of both the mature minor and their parents/guardians should be carefully explained during the assessment before testing.
- If a mature minor is identified as having Friedreich ataxia before the onset of symptoms, they and their family should receive immediate post-test counseling and psychosocial support and be the individual should be referred for neurological and heart care.

We also suggest that brothers and sisters of an affected person, who are under the age of 18 and do not have symptoms of Friedreich ataxia or have not undergone genetic testing, should have a heart ultrasound and electrocardiogram to look for heart problems that may require treatment. This is to ensure that any heart problems can be treated even though the child has not undergone genetic testing.

If in the future, a therapy is found that delays or slows symptoms of Friedreich ataxia, the brothers and sisters of the person with Friedreich ataxia should be tested regardless of whether they have symptoms, so that the therapy can be started as soon as possible.

What does this mean for you as a person living with Friedreich ataxia or caring for someone living with Friedreich ataxia?

It might be important for you to speak with your healthcare professional about testing for Friedreich ataxia and what it means for you and your child. In some places, national regulations do not allow pre-symptomatic testing of minors. If that is the case, your healthcare professional will be able to advise you and your children.

Who is this recommendation specifically for?

These recommendations are specifically for brothers or sisters aged under 18 years of individuals with Friedreich ataxia and parents or guardians of children with Friedreich ataxia.

11.4 Management of testing for other relatives of a person with Friedreich ataxia

11.4.1 Testing of other relatives

Table 11.1 lists the risk of being a carrier and the risk of having an affected child for a person with FRDA and their relatives. The calculated risk of having an affected child assumes that the partner of the individual with FRDA is unrelated and Caucasian, with a risk of being a carrier of 1 in 85. If the individual's partner is related to them, the risk is likely to be considerably higher and needs to be calculated individually. If a relative is identified as a carrier, their partner should be offered carrier testing for the GAA expansion and the implications for reproductive planning should be discussed. If the partner is not a carrier of a GAA expansion, the risk that they are a carrier of a point mutation/deletion is about 1 in 4000 and the risk of having an affected child is about 1 in 16,000 (i.e., about double the risk of a Caucasian couple without a family history of FRDA). Sequencing of *FXN* can be offered to the partner in this situation. The person undergoing sequencing needs to be made aware of the risk of finding a variant of unknown significance; that is, a DNA sequence change where it cannot be determined if it is a disease causing pathogenic variant or a benign polymorphism. Some laboratories will agree to only report pathogenic or likely pathogenic variants and not variants of uncertain significance in the setting of carrier screening.

It is recommended that carrier testing be first undertaken on the closest relative as a negative result means that genetic testing of more distant relatives may not be necessary.

11.4.2 Reproductive options for carrier couples

Options available to couples where both are carriers of *FXN* pathogenic variants are as follows. Some or all of these options may not be available in some centers.

Prenatal diagnosis: this is generally done by chorionic villus sampling (CVS). Here the chorion (part of the developing placenta) is biopsied under ultrasound guidance. This tissue generally contains the same genome as the fetus. Less commonly, prenatal diagnosis is done using amniocentesis, where amniotic fluid is removed under ultrasound guidance. If the fetus is found to have two *FXN* pathogenic variants, the couple has the option of pregnancy termination. However, if the couple choose not to terminate the pregnancy, this is equivalent to pre-symptomatic testing of a minor. The issues discussed above in relation to pre-symptomatic testing of a minor are relevant to this situation and appropriate counseling is required.

Preimplantation genetic testing (PGT-M): In vitro fertilization is undertaken whereby the woman's ovum is fertilized *in vitro* by the man's sperm using intracytoplasmic sperm injection. The fertilized cell is allowed to multiply, resulting in a multicellular embryo. At this point, one or more cells are biopsied and tested for the presence of *FXN* pathogenic variants. This is generally done by an indirect linkage method called karyomapping, since it is not technically possible to identify large

triplet repeat expansions in DNA from a single or few cells. Only embryos with one or no *FXN* pathogenic variants are available to be placed in the woman's uterus. The fact that the chance of pregnancy is as low as 20% for each PGT cycle should be discussed with the couple. Since PGT is less accurate than prenatal diagnosis, couples are generally offered prenatal diagnosis following PGT.

Donor ovum, sperm or embryo: the use of donor gametes or embryos where the donor(s) are not carriers of a *FXN* pathogenic variant will greatly reduce the risk of a child being born with FRDA. If possible, the gamete or embryo donors should be tested for the *FXN* GAA expansion to ensure they are not a carrier and therefore the risk of FRDA in the child is low.

Adoption: this is an option that some couples will choose where the above options are unacceptable for various reasons.

Table 11.1: Carrier risk and risk of affected offspring for individuals with Friedreich ataxia and their relatives

Relationship to individual with Friedreich ataxia (proband)	Risk of being a carrier	Risk of an affected child
Proband	1 (homozygous)	1 in 170
Parents	1 (heterozygous)	1 in 4
Aunt/uncle	1 in 2	1 in 680
First cousin	1 in 4	1 in 1360
First cousin once removed	1 in 8	1 in 2720
Second cousin	1 in 16	1 in 5440

Best practice statement

Carrier testing should be first undertaken on the closest relative as a negative result means that genetic testing of more distant relatives may not be necessary.

11.5 Management of questions related to GAA repeat size in Friedreich ataxia

Clinicians are often asked by affected individuals and/or parents for the size of GAA repeats that have been identified as the cause of that person's FRDA. This information should be supplied, but an explanation of the significance of the repeat sizes should be provided. An important point that should be discussed is that whilst larger GAA1 repeat sizes are, on average, associated with a more severe phenotype, at an individual level this information cannot be used to accurately predict phenotype or prognosis.

Recommendation

Should (where available) GAA repeat size used for counseling versus not using GAA repeat size for counseling be used for pre-symptomatic testing of individuals at risk of Friedreich ataxia?	**Strength**	**Level of evidence**
Although not all testing laboratories report *FXN* GAA repeat sizes, we suggest that when repeat sizes are reported for pre-symptomatic testing for Friedreich ataxia and the individual is homozygous for *FXN*	↑	⊕◯◯◯

GAA expansions, this information is provided to the tested individual upon request. Where GAA repeat sizes are provided to the tested individual we suggest that the individual is informed that there is a negative correlation between GAA1 size and age at onset, but the range of age of onset for any GAA1 size is broad and the age of onset for that person cannot be predicted with certainty.		
Justification: There are data that clearly demonstrate an inverse correlation between the smaller GAA repeat size (GAA1) and age of symptom onset in Friedreich ataxia, explaining approximately 40% of the variation in age of onset (3-5). General advice can be given based on these data, but a making a precise estimate of age of onset based on GAA1 repeat size is not possible.		
Subgroup considerations: This recommendation is for at-risk individuals undergoing pre-symptomatic genetic testing for Friedreich ataxia.		

Lay summary

Lay summary of clinical recommendation for managing questions related to GAA repeat size in Friedreich ataxia

Why this recommendation?

Looking at the averages over a large number of people with Friedreich ataxia, there is a relationship between the number of repeats on the smaller of the two *FXN* genes (GAA1) and the age at which a person first shows symptoms of Friedreich ataxia, as well as the occurrence of some features of the condition including cardiomyopathy and diabetes. That is, the bigger GAA1 is (the larger the number of repeats), the earlier symptoms will occur, on average.

We suggest that, when requested, individuals with Friedreich ataxia are provided with information about their repeat sizes. They should also be informed that it is not possible to make a precise estimate about when symptoms will appear and what other features will be present based on the GAA1 repeat size.

What does this mean for you as a person living with Friedreich ataxia or caring for someone living with Friedreich ataxia?

It might be important for you to speak with your healthcare professional about obtaining information about GAA repeat sizes and what it means for you or your child.

Who is this recommendation specifically for?

This recommendation is specifically for individuals with Friedreich ataxia and parents or guardians of children with Friedreich ataxia.

11.6 Optimal genetic support services for individuals with Friedreich ataxia and their families

As there are no specific clinical studies to inform the practice of genetic counseling in relation to FRDA, these guidelines are based on standard genetic counseling practice and the consensus of the expert authors of this chapter.

When an individual is diagnosed with FRDA, referral to a clinical geneticist or genetic counselor should be considered and the following issues should be discussed:

- Autosomal recessive inheritance and the genetic mechanism of FRDA.
- The implications for other family members, including:

- 1-in-4 risk of FRDA in siblings (existing and future)
- risk of FRDA for the offspring of the affected individual (generally relevant to older teenagers and adults)
- carrier risk and availability of testing for relatives
- availability of reproductive options where both members of a couple are identified as carriers.

The benefits of accurate genetic counseling include informed decision-making about testing for carrier status and reproductive options. It can also assist families in making decisions about testing for asymptomatic minors. The process can be of psychosocial benefit in dealing with the impact of being diagnosed (or a child being diagnosed) with FRDA.

The process of genetic counseling can also assist with managing the potential harms associated with genetic testing for affected or carrier status. Identifying that an asymptomatic individual will develop symptoms of FRDA through a genetic test may cause significant psychological morbidity, particularly if the individual was having testing to define carrier status and thus was not psychologically prepared for such an outcome. Identifying an individual as a carrier may cause short-term psychological morbidity, although studies of testing in other conditions show that being found to be a carrier rarely has major psychological impacts, particularly if that person's partner is found to not be a carrier.

The services required to ensure high quality genetic diagnosis and counseling include a clinical genetics service and access to laboratory testing for the *FXN* GAA repeat and *FXN* point mutations/deletions.

Best practice statements

Referral to a clinical geneticist or genetic counselor should be considered on diagnosis of Friedreich ataxia.
All individuals identified pre-symptomatically and their families would benefit from immediate post-test counseling and psychosocial support and referral for appropriate neurological and cardiac surveillance.
There is no evidence to support routine use of any pharmacological therapies in patients diagnosed with Friedreich ataxia pre-symptomatically.

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