

QUESTION

Should offering testing vs. not offering testing be used for mature minors at risk of Friedreich ataxia?

POPULATION:	mature minors at risk of Friedreich ataxia
INTERVENTION:	offering testing
COMPARISON:	not offering testing
MAIN OUTCOMES:	Psychological harm/benefit/anxiety; Discrimination;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>There is one study that examined the views of individuals with FRDA and parents of individuals with FRDA about testing of asymptomatic immature and mature minor siblings of people with FRDA (Lowe et al, 2015). There were four findings that emerged from this qualitative study. 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, participants felt it was not the clinician's role to make a final decision about whether testing occurs. Finally, a specific issue of concern regarding testing was what and when to tell at-risk children about the test result.</p>	<p>The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of genetic testing of minor siblings.</p> <p>2/7 indicated that the problem was serious, 2/7 indicated probably serious, 1/7 indicated they didn't know if serious, 2/7 indicated varied or sometimes serious.</p> <p>2/7 indicated that the problem was urgent, 2/7 indicated probably not urgent, 2/7 indicated they didn't know if urgent, 1/7 indicated varied or sometimes serious.</p> <p>2/7 indicated that the problem was a priority, 2/7 indicated probably not a priority, 2/7 indicated they didn't know if a priority, 1/7 indicated varied or sometimes a priority. (Aug 2020)</p>

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Trivial <input type="radio"/> Small <input type="radio"/> Moderate <input checked="" type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>A search of four databases (CENTRAL, MEDLINE, EMBASE, PsycINFO) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 20 August 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.</p>	<p>If a mature minor sibling of a person with FRDA is tested for their <i>FXN</i> genetic status and is not homozygous/compound heterozygous for pathogenic variants then they will not develop FRDA and this will generally result in relief of anxiety for the individual and their family. If they have homozygous/compound heterozygous <i>FXN</i> pathogenic variants then they can have surveillance for cardiac involvement.</p>

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ● Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know 	<p>A search of four databases (CENTRAL, MEDLINE, EMBASE, PsycINFO) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 20 August 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.</p>	<p>If the individual has homozygous/compound heterozygous <i>FXN</i> pathogenic variants this is very likely to result in anxiety for the individual and their family. Some individuals not homozygous/compound heterozygous may have some negative response to this finding due to the phenomenon of "survivor guilt".</p>

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High ● No included studies 	<p>No published evidence.</p>	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS									
<ul style="list-style-type: none"> ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability 	<table border="1"> <thead> <tr> <th>Outcomes</th> <th>Importance</th> <th>Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Psychological harm/benefit/anxiety - not measured</td> <td>CRITICAL^a</td> <td>-</td> </tr> <tr> <td>Discrimination - not measured</td> <td>IMPORTANT^b</td> <td>-</td> </tr> </tbody> </table>	Outcomes	Importance	Certainty of the evidence (GRADE)	Psychological harm/benefit/anxiety - not measured	CRITICAL ^a	-	Discrimination - not measured	IMPORTANT ^b	-	
Outcomes	Importance	Certainty of the evidence (GRADE)									
Psychological harm/benefit/anxiety - not measured	CRITICAL ^a	-									
Discrimination - not measured	IMPORTANT ^b	-									

	<ul style="list-style-type: none"> a. Identified as critical by expert authors on this topic. b. Identified as important by expert authors on this topic. 	
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Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input checked="" type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know 	No published evidence.	<p>A survey designed to systematically collect expert-based opinions from clinicians involved in developing the recommendations for this topic and providing clinical care for individuals with Friedreich ataxia, was conducted. Clinical experts from Australia, Europe, UK, South America, Canada and the USA were asked to consider the harms/benefits of Testing as a management strategy for mature minors at risk of Friedreich ataxia.</p> <p>Reflecting on the impact of Testing on <u>Psychological harm/benefit/anxiety</u>, 100% (4/4) clinical experts reported a benefit (large, moderate or small), and 0% (0/4) reported observing a harm (large, moderate or small). Reflecting on the impact on <u>Discrimination</u>, 0% (0/4) clinical experts reported a benefit, 50% (2/4) reported no effect and, 50% (2/4) reported observing a harm.</p>

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 	No published evidence.	

SUMMARY OF JUDGEMENTS

JUDGEMENT

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
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CONCLUSIONS

Recommendation

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 FRDA 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.

Research priorities

This is a research area of high priority.

Reference

Lowe GC, Corben LA, Duncan RE, Yoon G, Delatycki MB. "Both sides of the wheelchair": The views of individuals with, and parents of individuals with Friedreich ataxia regarding pre-symptomatic testing of minors. *J Genet Couns.* 2015;24(5):732-43.