

## QUESTION

Should screening of Vitamin D and bone specific markers vs. no screening/risk-stratified screening be used for all patients with Friedreich ataxia?

POPULATION:	all patients with Friedreich ataxia
INTERVENTION:	screening of Vitamin D and bone specific markers
COMPARISON:	no screening/risk-stratified screening
MAIN OUTCOMES:	Bone mineral density;

## ASSESSMENT

### Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input checked="" type="radio"/> Probably yes</li> <li><input type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	<p>Data from the FA Clinical Outcome Measures (FA-COMS) registry found 2.1% (23/1104) people with FRDA reported osteoporosis or osteopenia, while 9.7% (107/1104) reported a fracture. None of these were vertebral/spinal or femoral fractures. <a href="https://clinicaltrials.gov/ct2/show/NCT03090789">https://clinicaltrials.gov/ct2/show/NCT03090789</a></p> <p>A small pilot cross sectional study (n=28) showed that a majority of individuals with FRDA presented with low 25-OH vitamin D levels: 11 with reduced and 7 with deficient levels (Eigentler et al, 2014). We expect that a substantial proportion of individuals with FRDA will have low aBMD.</p>	<p>The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of osteoporosis.</p> <p>4/7 indicated that the problem was serious, 1/7 indicated probably serious, 2/7 indicated they didn't know if serious.</p> <p>2/7 indicated that the problem was urgent, 3/7 indicated probably not urgent, 2/7 indicated they didn't know if urgent.</p> <p>2/7 indicated that the problem was a priority, 1/7 indicated probably a priority, 2/7 indicated probably not a priority, 2/7 indicated they didn't know if priority. (Aug 2020)</p>

### Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li><input type="radio"/> Trivial</li> <li><input type="radio"/> Small</li> <li><input checked="" type="radio"/> Moderate</li> <li><input type="radio"/> Large</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	<p>A search of three databases (CENTRAL, MEDLINE, EMBASE) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 04 November 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.</p> <p>Recent consensus statements in children (e.g., Galindo-Zavala et al, 2020) highlight the potential utility of winter vitamin D screening to identify relevant deficiency in these populations and complement the available data in adults with FRDA (Eigentler et al, 2014).</p>	<p>Screening of Vitamin D is likely to identify a need for supplementation that could slow loss of aBMD and progression to osteopenia/osteoporosis. Addressing nutritional deficiencies is a cornerstone of optimizing bone health.</p>

--	--	--

## Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Large</li> <li>○ Moderate</li> <li>○ Small</li> <li>● Trivial</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>A search of three databases (CENTRAL, MEDLINE, EMBASE) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 04 November 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.</p>	<p>Vitamin D could be included in annual screening studies, e.g., for FRDA-related DM, thus screening is unlikely to be inconvenient for patients/families.</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"> <li>○ Very low</li> <li>● Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	<p>No published evidence.</p> <p>Recent consensus statements in children (e.g., Galindo-Zavala et al, 2020) highlight the potential utility of winter vitamin D screening to identify relevant deficiency in these populations and complement the available data in adults with FRDA (Eigentler et al, 2014).</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"> <li>○ Important uncertainty or variability</li> <li>○ Possibly important uncertainty or variability</li> <li>● Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> </ul>	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="background-color: #D3D3D3;">Outcomes</th> <th style="background-color: #D3D3D3;">Importance</th> <th style="background-color: #D3D3D3;">Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Bone mineral density - not measured</td> <td>IMPORTANT<sup>a</sup></td> <td style="text-align: center;">-</td> </tr> </tbody> </table>	Outcomes	Importance	Certainty of the evidence (GRADE)	Bone mineral density - not measured	IMPORTANT <sup>a</sup>	-	
Outcomes	Importance	Certainty of the evidence (GRADE)						
Bone mineral density - not measured	IMPORTANT <sup>a</sup>	-						

	a. Identified as critical (1/6), important (3/6) and low importance (2/6) by people with FA and important by expert authors on this topic.	
--	--	--

## 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"> <li><input type="radio"/> Favors the comparison</li> <li><input type="radio"/> Probably favors the comparison</li> <li><input type="radio"/> Does not favor either the intervention or the comparison</li> <li><input checked="" type="radio"/> Probably favors the intervention</li> <li><input type="radio"/> Favors the intervention</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	<p>No published evidence.</p> <p>Recent consensus statements in children (e.g., Galindo-Zavala et al, 2020) highlight the potential utility of winter vitamin D screening to identify relevant deficiency in these populations and complement the available data in adults with FRDA (Eigentler et al, 2014).</p>	

## Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	<p>No published evidence.</p>	<p>The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if screening of Vitamin D levels and other bone specific markers was acceptable (weighing up the balance between benefits, harms and costs).</p> <p>3/3 indicated the intervention was acceptable. (Aug 2020).</p>

## SUMMARY OF JUDGEMENTS

PROBLEM	JUDGEMENT						
	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	<b>Moderate</b>	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	<b>Trivial</b>		Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	Very low	<b>Low</b>	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	<b>Probably no important uncertainty or variability</b>	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	<b>Probably favors the intervention</b>	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	<b>Yes</b>		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 ○	<b>Conditional recommendation for the intervention ●</b>	Strong recommendation for the intervention ○
---	--	---	--	---

## CONCLUSIONS

### Recommendation

We conditionally recommend screening for vitamin D deficiency over no screening or risk-stratified screening in individuals with Friedreich ataxia.

### Justification

Since assessment of vitamin D is done through venipuncture and is generally available (e.g., during routine laboratory assessments in FRDA such as glucose, HbA1c), along with the wide availability of supplementation with vitamin D, we conditionally recommend assessing vitamin D levels as a basis for supplementation if needed.

### Subgroup considerations

This recommendation is for all individuals with Friedreich ataxia. As vitamin D levels are dependent on several variables (time/season of year during assessment, degree of latitude, activity outdoor), screening might be more widely used in corresponding conditions (e.g., high latitude – low sun exposure, low activity outdoors). Additionally, in individuals found to meet age-specific criteria for osteoporosis, additional screening for markers of bone mineral metabolism could be considered as part of a dedicated bone health evaluation.

## Research priorities

A systemic evaluation of vitamin D levels in a large cohort of individuals with FRDA could refine estimates of the prevalence of vitamin D insufficiency and deficiency. Further, studies could evaluate the potential effect of supplementation strategies (individualized based on level vs. universal supplementation) and the impact of supplementation on clinically relevant bone health outcomes.

### References

Eigentler A, Nachbauer W, Donnemiller E, Poewe W, Gasser RW, Boesch S. Low bone mineral density in Friedreich ataxia. *Cerebellum*. 2014;13(5):549-57.

Galindo-Zavala R, Bou-Torrent R, Magallares-Lopez B, Mir-Perello C, Palmou-Fontana N, Sevilla-Perez B, et al. Expert panel consensus recommendations for diagnosis and treatment of secondary osteoporosis in children. *Pediatr Rheumatol Online J*. 2020;18(1):20.

Lynch D. FA Clinical Outcome Measures (FA-COMS) Registry (unpublished data): [clinicaltrials.gov](https://clinicaltrials.gov); 2017 [Available from: <https://clinicaltrials.gov/ct2/show/NCT03090789>