QUESTION

Should universal screening (DXA + DXA or other VF assessment) vs. risk-stratified screening assessment (DXA + DXA or other VF assessment) be used for children with Friedreich ataxia?	
POPULATION:	children with Friedreich ataxia
INTERVENTION:	universal screening (DXA + DXA or other VF assessment)
COMPARISON:	risk-stratified screening assessment (DXA + DXA or other VF assessment)
MAIN OUTCOMES:	Diagnosis of low BMD/osteoporosis; Fractures; Acute care utilization; Health-related quality of life;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	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 (Lynch, 2017). Although clinical experience suggests that some children with FRDA do have low aBMD Z-score (<= -2.0), the prevalence of low bone mineral density in children with FRDA remains unknown. However, FRDA shares similarities with other chronic conditions with decreased ambulation (e.g., neuromuscular disorders) where decreases in aBMD Z-score have been reported.	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of osteoporosis. 4/7 indicated that the problem was serious, 1/7 indicated probably serious, 2/7 indicated they didn't know if serious. 2/7 indicated that the problem was urgent, 3/7 indicated probably not urgent, 2/7 indicated they didn't know if urgent. 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)

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	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. Recent consensus statements (e.g., Simm et al, 2018; Galindo-Zavala et al, 2020) highlight the potential utility of DXA in other similar conditions where risk for secondary osteoporosis may be increased, and DXA results may influence treatment decisions.	Skeletal site selection in pediatric DXA is typically recommended to include lumbar spine and total body less head; distal femur may also be appropriate for those with contractures. Scoliosis and scoliosis rods may impact DXA assessment in individuals with FRDA, requiring expert interpretation. Imaging may also be recommended for vertebral pathology.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	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. DXA scan results may lead to additional anxiety and stress, and additional referrals and care utilization. Z-scores may be decreased in some children related to delays in maturation. The potential for over-diagnosis and over-treatment should be considered.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	No published evidence. Recent consensus statements (e.g., Simm et al, 2018; Galindo-Zavala et al, 2020) highlight the potential utility of DXA in other similar conditions where risk for secondary osteoporosis may be increased, and DXA results may influence treatment decisions.	

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		

Outcomes	Importance	Certainty of the evidence (GRADE)
Diagnosis of low BMD/osteoporosis - not measured	IMPORTANT[a]	-
Fractures - not measured	CRITICAL[b]	-
Acute care utilization - not measured	CRITICAL[c]	-
Health-related quality of life - not measured	IMPORTANT[d]	-

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. b. Identified as critical (4/6) and important (2/6) by people with FA and important by expert authors on this topic. c. Identified as critical (4/6) and low importance (2/6) by people with FA and critical by expert authors on this topic. d. Identified as critical (2/6) and important (4/6) 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
○ 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	No published evidence. Recent consensus statements (e.g., Simm et al, 2018; Galindo-Zavala et al, 2020) highlight the potential utility of DXA in other similar conditions where risk for secondary osteoporosis may be increased, and DXA results may influence treatment decisions. The most appropriate timing for initiation of universal screening is challenging to ascertain. The utility of universal screening may be lower in individuals with FRDA who have a relatively low burden of comorbidities and minimal limits to ambulation, although there are not yet data to guide this decision.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No published evidence in FRDA. Additional screening recommendations do add burden in time to patients/families.	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if screening assessments of osteoporosis for all children were acceptable (weighing up the balance between benefits, harms and costs). 1/3 indicated the intervention was acceptable, 1/3 indicated probably acceptable, 1/3 indicated varied or sometimes acceptable. (Aug 2020).

SUMMARY OF JUDGEMENTS

	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

	JUDGEMENT						
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
○	○	○	●	○

CONCLUSIONS

Recommendation

Clinicians should consider universal screening of children with Friedreich ataxia for low bone density via DXA; at minimum, a risk-stratified approach is recommended.

Justification

Recent consensus statements (Simm et al, 2018; Galindo-Zavala et al, 2020) highlight the potential utility of DXA in other similar conditions where risk for secondary osteoporosis may be increased, and DXA results may influence treatment decisions. The most appropriate timing for initiation of universal screening is not clear. The utility of universal screening may be lower in individuals with FRDA who have a relatively low burden of comorbidities and minimal limits to ambulation, although there are not yet data to guide this decision. The initial DXA scan could be ordered by the primary care physician or FRDA specialist. If low bone mineral density is diagnosed, children with FRDA should be managed by a clinician with relevant clinical experience, such as a pediatric endocrinologist.

Subgroup considerations

This recommendation is for children with Friedreich ataxia. The most appropriate screening strategy may depend on the age and pubertal status of the child; the longitudinal trajectory of aBMD Z-score and/or absolute aBMD or BMC, DXA and/or related imaging results; an integrated assessment of fall risk; as well as priorities of patients and families. Routine skeletal sites in pediatric DXA scans include the lumbar spine and total body less head (ISCD, 2019). Additional sites could be evaluated based on age, clinical history, and local expertise.

Research priorities

Assessment of the prevalence of clinically relevant low aBMD in children with FRDA is needed. Critically, natural history studies are also needed to determine the impact of FRDA on aBMD, skeletal development, and fracture incidence across the lifespan.

Reference

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.

International Society for Clinical Densitometry (ISCD). 2019 ISCD Official Positions: Pediatric: ISCD; 2019 [Available from: https://iscd.org/learn/official-positions/pediatric-positions/.

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

Simm PJ, Biggin A, Zacharin MR, Rodda CP, Tham E, Siafarikas A, et al. Consensus guidelines on the use of bisphosphonate therapy in children and adolescents. J Paediatr Child Health. 2018;54(3):223-33.