QUESTION

Should universal screening assessment (DXA + DXA or other vertebral fracture assessment) vs. risk-stratified screening assessment (DXA + DXA or other VF assessment) be used for adults with Friedreich ataxia?	
POPULATION:	adults with Friedreich ataxia
INTERVENTION:	universal screening assessment (DXA + DXA or other vertebral fracture 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). However, self-reported data likely give an underestimate of the prevalence of impaired bone health, since many individuals may not have undergone screening procedures. A small pilot cross sectional study (n=28) evaluating the prevalence of low bone mineral density in FA revealed a prevalence rate of about 20% of a bone mineral density below the expected range for age (Eigentler et al, 2014).	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. However, there are approved therapies for use to treat low aBMD and potentially prevent fractures in adults with secondary osteoporosis, as may occur in FRDA. Thus, detecting low aBMD is clinically	The detection of low bone mineral density in FRDA and a consequently initiated treatment may prevent fall-related fractures.

	actionable.	

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. Medications have adverse effects, and to our knowledge adverse effects related to osteoporosis treatment have not been studied in FRDA. Also, medications may be expensive. On balance, preventing fracture is expected to make medication use cost-effective, but cost-effectiveness of osteoporosis medications has not been studied in FRDA.	

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 in FRDA. However, osteoporosis medications have been studied extensively in adults with primary and secondary forms of osteoporosis.	

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 research. However, osteoporosis medications have been studied extensively in adults with primary and secondary forms of osteoporosis. Clinicians with expertise in FRDA generally note the availability of evidence in related disorders but the lack of FRDA specific research.	A survey designed to systematically collect expert-based opinions from clinicians involved in the development of these guidelines 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 evaluating for low bone mineral density with a DXA if patients have had at least two lifetime fractures as a management strategy for children (under 18y) OR adults (18y+). Reflecting on the impact of **evaluating for low bone mineral density with a DXA if patients have had at least two lifetime factures** on diagnosis of low BMD/osteoporosis, 48% (12/25) clinical experts reported a benefit (large, moderate or small), 0% (0/25) reported no effect and, 0% (0/25) reported observing a harm (large, moderate or small). 13 clinicians could not provide any information on this outcome. Reflecting on the impact on factures, 44% (11/25) clinical experts reported a benefit, 4% (1/25) reported no effect and, 0% (0/25) reported observing a harm. 13 expert clinicians could not provide any information on this outcome. Reflecting on the impact on acute care utilization,

		44% (11/25) clinical experts reported a benefit, 4% (1/25) reported no effect and, 0% (0/25) reported observing a harm. 13 expert clinicians could not provide any information on this outcome. Reflecting on the impact on health related QOF, 48% (12/25) clinical experts reported a benefit, 0% (0/25) reported no effect and, 0% (0/25) reported observing a harm. 13 expert clinicians could not provide any information on this outcome. Reflecting on the impact of **evaluating for low bone mineral density with a DXA if patients have had one potentially pathologic fracture (for example factures of the hip or spine)** on diagnosis of low BMD/osteoporosis, 52% (13/25) clinical experts reported a benefit (large, moderate or small), 0% (0/25) reported no effect and, 0% (0/25) reported observing a harm (large, moderate or small). 12 clinicians could not provide any information on this outcome. Reflecting on the impact on factures, 52% (13/25) clinical experts reported a benefit, 0% (0/25) reported no effect and, 0% (0/25) reported observing a harm. 12 expert clinicians could not provide any information on this outcome. Reflecting on the impact on acute care utilization, 48% (12/25) clinical experts reported a benefit, 4% (1/25) reported no effect and, 0% (0/25) reported observing a harm. 12 expert clinicians could not provide any information on this outcome. Reflecting on the impact on health related QOF, 52% (13/25) clinical experts reported a benefit, 0% (0/25) reported no effect and, 0% (0/25) reported observing a harm. 12 expert clinicians could not provide any information on this outcome. Reflecting on the impact of **evaluating for low bone mineral density with a DXA at diagnosis, and then every 2-5 years** on diagnosis of low BMD/osteoporosis, 44% (11/25) clinical experts reported a benefit (large, moderate or small), 8% (2/25) reported no effect and, 0% (0/25) reported observing a harm (large, moderate or small). 12 clinicians could not provide any information on this outcome. Reflecting on the impact on factures, 36% (9/25) clinical experts reported a benefit, 16% (4/25) reported no effect and, 0% (0/25) reported observing a harm. 12 expert clinicians could not provide any information on this outcome. Reflecting on the impact on acute care utilization, 36% (9/25) clinical experts reported a benefit, 16% (4/25) reported no effect and, 0% (0/25) reported observing a harm. 12 expert clinicians could not provide any information on this outcome. Reflecting on the impact on health related QOF, 40% (10/25) clinical experts reported a benefit, 12% (3/25) reported no effect and, 0% (0/25) reported observing a harm. 12 expert clinicians could not provide any information on this outcome. Reflecting on the impact of e**valuating for low bone mineral density with a DXA when patients become non-ambulatory, then every 2-5 years** on diagnosis of low BMD/osteoporosis, 44% (11/25) clinical experts reported a benefit (large, moderate or

		small), 4% (1/25) reported no effect and, 0% (0/25) reported observing a harm (large, moderate or small). 13 clinicians could not provide any information on this outcome. Reflecting on the impact on factures, 40% (10/25) clinical experts reported a benefit, 8% (2/25) reported no effect and, 0% (0/25) reported observing a harm. 13 expert clinicians could not provide any information on this outcome. Reflecting on the impact on acute care utilization, 36% (9/25) clinical experts reported a benefit, 12% (3/25) reported no effect and, 0% (0/25) reported observing a harm. 13 expert clinicians could not provide any information on this outcome. Reflecting on the impact on health related QOF, 40% (10/25) clinical experts reported a benefit, 8% (2/25) reported no effect and, 0% (0/25) reported observing a harm. 13 expert clinicians could not provide any information on this outcome. Reflecting on the impact of **not screening for low bone mineral density** on diagnosis of low BMD/osteoporosis, 0% (0/25) clinical experts reported a benefit (large, moderate or small), 4% (1/25) reported no effect and, 44% (11/25) reported observing a harm (large, moderate or small). 13 clinicians could not provide any information on this outcome. Reflecting on the impact on factures, 0% (0/25) clinical experts reported a benefit, 4% (1/25) reported no effect and, 44% (11/25) reported observing a harm. 13 expert clinicians could not provide any information on this outcome. Reflecting on the impact on acute care utilization, 0% (0/25) clinical experts reported a benefit, 8% (2/25) reported no effect and, 40% (10/25) reported observing a harm. 13 expert clinicians could not provide any information on this outcome. Reflecting on the impact on health related QOF, 0% (0/25) clinical experts reported a benefit, 12% (3/25) reported no effect and, 36% (9/25) reported observing a harm. 13 expert clinicians could not provide any information on this outcome.

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 research.	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if screening assessments of osteoporosis for all adults were acceptable (weighing up the balance between benefits, harms and costs). 2/3 indicated the intervention was acceptable, 1/3 indicated probably 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
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

We recommend universal screening assessment of bone mineral density (DXA scan, fracture history) over risk-stratified screening in adults with Friedreich ataxia, given the availability of anti-osteoporosis medications that have been shown to prevent pathological fractures due to low bone mineral density (osteopenia, osteoporosis) in related populations.

Justification

Although there are no randomized controlled trials, we recommend screening of bone mineral density in FRDA since the prevalence of low aBMD in the FRDA population might be underestimated and is at least 20% according to a small cross-sectional study (Eigentler et al, 2014). Radiation exposure during a DXA scan is extremely low and therefore considered trivial. Determining low aBMD and initiating a corresponding therapy/prophylaxis will potentially prevent fall-related fractures and could maintain or improve quality of life and prolong capacity for ambulation. The initial DXA scan could be ordered by a primary care physician or FRDA specialist. If osteoporosis is diagnosed, adults with FRDA should be managed by clinicians with relevant clinical experience, such as an endocrinologist.

Subgroup considerations

This recommendation is for adults with Friedreich ataxia. The mobility status of individuals with Friedreich ataxia might be important in terms of bone mineral density, since in a small cross-sectional study there was a significantly lower aBMD in the femoral neck in individuals with FRDA who use wheelchairs, probably related to immobility. Measurement of forearm aBMD and/or distal femur could complement routine assessments (spine and hip, as per ISCD 2019) in individuals who are mostly non-ambulatory as these skeletal sites have yielded additional insights in related populations.

Annual DXA assessment could be considered for individuals found to have low bone density for age on the initial DXA and/or in whom the DXA results would guide further management decisions. The frequency may be adjusted based upon trends in BMD and with input of a bone health specialist. For individuals found to have BMD within the expected range for age, consideration should be given to repeating DXA in 2-3 years, or sooner as indicated by a clinical change (such as change in mobility status, use of new medications that could impact bone health, new fracture history).

Research priorities

A systemic evaluation of bone health (DXA scans, lab parameters, fracture history) in a large cohort of individuals with FRDA (stratified by mobility status, i.e., mostly ambulatory vs. mostly using wheelchair) would be useful to generate better estimates.

References

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