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Consensus Guideline für Klinisches Management der Friedreich's Ataxie

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Consensus Clinical Management Guidelines for Friedreich's ataxia

Guidelines for clinicians, patients and research to ensure better outcomes today, and for the future.

Murdoch Childrens Research Institute | UNIKLINIK RWTH AACHEN | THE CHILDREN'S HOSPITAL of PHILADELPHIA | ULB UNIVERSITÉ LIBRE DE BRUXELLES | FARA Friedreich's Ataxia Research Alliance

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Disclaimer: This document is designed to be a general guide to appropriate clinical practice. It is anticipated it will be followed subject to the clinician's judgment and the preference of the person with Friedreich ataxia in each individual case. These guidelines are designed to provide information to assist in decision-making and are based on the best evidence available at the time of development. Clinicians and individuals with Friedreich ataxia are encouraged to ensure they are aware of evidence that may become available after the completion of this document. Copies of the document can be downloaded through the Friedreich Ataxia Research Alliance (USA) on: http://www.curefa.org/

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Friedreich ataxia clinical management guidelines

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Abstract

Friedreich ataxia (FRDA), a multisystem autosomal recessive disease, is the most common inherited ataxia, affecting approximately 1 in 29,000 individuals. The hallmark clinical features of FRDA include progressive ataxia, spasticity, absent lower limb reflexes, impaired vibration sense and proprioception, scoliosis, foot deformity and cardiomyopathy. Despite significant progress in the search for disease modifying agents, the chronic, progressive nature of FRDA continues to have a profound impact on the health and well-being of people with FRDA. At present there is no proven treatment that can slow the progression or eventual outcome of this life-shortening condition.

Given the focus on identifying disease-modifying agents, clinical management and intervention in FRDA has to date, received little attention. This document presents clinical guidelines specific to FRDA to ensure consistency in the delivery of health services to people with FRDA. In addition this document aims to identify gaps in current evidence that present opportunity for further research.

Thirty-nine clinicians located in Europe, UK, Australia and the USA with expertise in FRDA contributed to the writing of these guidelines. Contributing authors critically appraised the published evidence related to FRDA clinical care and provided this evidence in a concise manner in order to guide clinicians treating people with FRDA. Evidence was evaluated according to the recommendations of the Guidelines International Network (http://www.g-i-n.net/). Recommendations included in the guidelines were established according to the criteria developed by the National Health and Medical Research Council (NHMRC) Australia. In the absence of robust evidence these guidelines make recommendations based on the collective expertise of the specialist working groups and in so doing, identify critical areas demanding further investigation.

Introduction

Statement of purpose

These guidelines have been compiled by thirty-nine clinicians with expertise in the clinical management of individuals with Friedreich ataxia (FRDA). The purpose of these guidelines is to critically appraise the published evidence related to FRDA clinical care and provide this evidence in a concise manner in order to guide clinicians treating people with FRDA. In the absence of robust evidence these guidelines make recommendations based on the collective expertise of the specialist working groups and in so doing, identify critical areas demanding further investigation.

Background

Despite significant progress in the search for disease modifying agents, the chronic, progressive nature of FRDA continues to have a profound impact on the capacity of affected individuals to participate in significant activities and roles in daily life.

In 2003, "*Revalidatie Geneeskundige Richtlijn Ataxie van Friedreich*" was written by a special task force under the auspices of '*Vereniging Spierziekten Nederland'.* These were the first attempt to write guidelines that provided an evidence base to management of people with FRDA. These guidelines were subsequently updated and adapted for international use in September 2007. In 2009, Ataxia UK launched "Management of ataxia: towards best clinical practice". This document was developed to provide recommendations for the management of people with inherited ataxia, including FRDA. Whilst this further initiative was welcomed, it was apparent that issues specific to FRDA require disease specific guidelines. Furthermore, it was apparent that the multiple gaps in evidence surrounding service delivery may provide a platform for ongoing research.

Process

In 2010, in consultation with international clinicians specializing in the management of people with FRDA, a list of clinical practice guideline topics were generated.

In February 2011 a successful application was made to Friedreich Ataxia Research Alliance (USA) for funding to support the development of clinical practice guidelines.

In May 2011 a face to face meeting of interested clinicians was held prior to the 4th International Friedreich's Ataxia Conference in Strasbourg, France. This meeting provided background information to clinicians, explained the process of developing the guidelines including the time commitment involved and planned the way forward including the process of communication between members of the specialist working group (i.e., teleconferences). At this meeting an executive committee was established to oversee the process of guideline development. Specialist working groups (SWGs) related to specific topics were also established. Each member of the SWGs was asked to formally declare any potential conflict of interest (Appendix 1) however none were present that required removal from the writing groups.

SWGs were provided with instruction on how to evaluate the evidence according to the recommendations of the Guidelines International Network (http://www.g-i-n.net/) (Appendix 2 and 3). SWGs were encouraged to consult widely with colleagues and peers to ensure consistency of evidence. Draft iterations of the guidelines were circulated to all authors involved in producing the guidelines for comment and feedback. The final draft was sent to peak bodies representing individuals with FRDA and clinicians for feedback. Each group was also provided with a format for developing the guidelines (Appendix 4). A range of international methods of grading of evidence and recommendations were reviewed. These included those recommended by the American Academy of Neurology (AAN) (USA), Scottish Intercollegiate Guidelines Network (SIGN), National Institute of Health and Clinical Excellence (NICE) (UK) and the National Health and Medical Research Council (NHMRC) Australia. Given no one method was identified as clearly superior, the guidelines were established according to the criteria developed by the NHMRC (Appendix 5). Elements of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) were incorporated where applicable however it should be noted that cost effectiveness was not a major consideration in the development of these guidelines as in the majority of the recommendations there was little evidence available. Where no clear Level I, II III or IV evidence was available but where there was sufficient consensus within the specialist working group, good practice points (GPP) were provided (1).

The following section provides an executive summary of recommendations from each chapter.

Executive Summary of Recommendations

2.1 Ataxia

Recommendations	Grading
Regular neurological examination should take place, and may guide referral to appropriate specialists in a timely fashion.	GPP
Physical therapy may be useful to help with balance, flexibility, accuracy of limb movements, and maintenance of strength.	GPP
Occupational therapy may identify risks for people with ataxia as well as help minimize difficulties in the performance of daily activities.	GPP
Routine orthopedic care is necessary to follow and treat orthopedic issues that can influence ataxia.	GPP

2.2 Weakness

Recommendations	Grading
Assessment of muscle weakness is an essential part of the functional evaluation of an individual with FRDA.	GPP
Fatigue is a prevalent symptom in FRDA that may be included in quality of life assessments of individuals with FRDA.	GPP

Physical therapy and exercise training may improve strength, motor performance and reduce fatigue.	GPP
Muscle weakness may interfere with the clinical assessment of coordination and gait in individuals with FRDA.	GPP
Medications improving mitochondrial function may improve muscle strength and reduce fatigue.	GPP

2.3 Neuropathy

Recommendations	Grading
Neuropathic pain may be treated with Gabapentin, Pregabalin, Lamotrigine, Amitriptyline or Duloxetine.	C (2, 3)
A detailed sensory assessment and examination will establish the extent of neuropathy.	GPP
Protective foot care is important.	GPP
Preventative measures such as review of daily activities, transfers and wheelchair positioning may reduce the incidence of focal neuropathies.	GPP

2.4 Spasticity and Spasm

Recommendations	Grading
People with FRDA may benefit from assessment for spasticity, pain and spasms (including nocturnal spasms) and incipient or established contracture. This may guide treatment.	GPP
On implementation of an anti-spasticity intervention, individuals with FRDA may benefit from reassessment as the treatment of spasticity can unmask weakness and cause deterioration in gait and standing transfers. Individuals should be warned of this phenomenon before anti-spasticity interventions are commenced.	GPP
Aggravating factors such as infection, pain, constipation, diarrhea, dehydration and pressure sores should be considered and treated in the context of acute onset or exacerbation of spasticity and/or ataxia.	GPP
Spasticity and spasms should be treated at an early stage, initially by non-pharmacological means. If these are unsuccessful, pharmacological means such as the use of Baclofen, Tizanidine, Benzodiazepines, Dantrolene sodium, Gabapentin, botulinum toxin injections, alcohol and phenol injections or intrathecal Baclofen pumps may be considered. The benefit of such compounds must be balanced against adverse effects they might produce on other symptoms of FRDA (for example ataxia). In the last resort, surgical options may be considered. The distribution of spasticity around the body may also determine which intervention is chosen.	C (4-6)
Individuals with FRDA, families and caregivers should be educated to monitor the development of spasticity and incipient contractures, and should be given an ongoing plan of exercises and passive or active stretching to be performed routinely outside the clinical setting.	C (4)

2.5 Restless Legs (RLS)

Recommendations	Grading
People with FRDA should be specifically asked if they have RLS symptoms	B (7, 8)
A full history of the symptoms should be taken from patients suspected of having RLS so that other confounding conditions i.e. periodic leg movements can be excluded.	B (9)
Secondary causes of RLS should be excluded, in particular, a drug history should be taken and serum ferritin should be undertaken.	B (9)
Initial treatment of RLS should consider the needs of the patient, the severity of the symptoms, the relative significance of the reported effects of the treatment and the level of dysfunction attributable to RLS.	A (10)

2.6 Mobility

Recommendations	Grade
Mobility, balance, core stability, trunk control, spasticity, foot position and strength should be assessed by a suitably qualified physical therapist.	GPP
The impact of spasticity of lower limbs on mobility should be evaluated when assessing gait.	GPP
Foot and ankle posture should be assessed by a suitably qualified physical therapist and treated proactively.	D (11, 12)
Strategies such as an appropriate exercise program, aquatic physical therapy and stretches may be implemented to prolong ambulation and reduce the number of falls in people with FRDA.	D (13, 14)
Individuals with FRDA dependent on a wheelchair for mobility may still benefit from rehabilitation to improve their mobility.	D (14)
Botulinum toxin and prescription of ankle-foot orthotics may be useful in reducing the impact of spasticity during mobility and will help maintain good foot alignment for mobility.	GPP
Gait aid provision may prolong the capacity to walk. A heavy/weighted gait-aid may be a beneficial for some individuals with FRDA.	GPP
Standing frame and tilt table may be used to maintain foot alignment to enable independent transfers.	GPP
An inpatient rehabilitation program may prolong mobility and transfer ability.	D (14)

2.7 Dysarthria

Recommendations	Grading
People with FRDA should undergo a comprehensive communication	C (15)

evaluation by a speech and language pathologist at the time of diagnosis or symptom onset and thereafter undertake review assessments to monitor performance.	
Instruction in environmental modification may be beneficial for individuals with motor speech difficulties.	C (16)
Participation in intensive and systematic behavior therapy may be beneficial to people with FRDA with dysarthria.	C (16)
Traditional non-systematic behavioral therapy may not be helpful for mitigating the effects of progressive dysarthria.	GPP

2.8 Dysphagia

Recommendations	Grading
People with FRDA should undergo a comprehensive swallowing evaluation by a speech and language pathologist at the time of diagnosis or symptom onset and thereafter to monitor performance.	D (17, 18)
Instruction in environmental modification and compensatory postures may be beneficial for individuals with dysphagia.	D (19-22)
Instruction in dietary modification may be beneficial for individuals with dysphagia.	D (21, 23, 24)
Traditional non-systematic behavioral therapy (e.g., oral motor therapy) may not be helpful for mitigating the effects of dysphagia.	GPP

2.9 Vision

Recommendations	Grade
Screening or testing as per country specific general vision screening guidelines should be applied to individuals with FRDA.	GPP
Memantine, Acetazolamide, Aminopyridine, Clonazepam, Gabapentin or Ondansetron may be of benefit in treating square wave jerks and ocular flutter.	D (25)

2.10 Bladder Dysfunction

Recommendations	Grading
Exclusion of a concomitant urinary tract infection and assessment of post micturition residual urine is recommended prior to commencement of treatment.	C (26, 27)
Antimuscarinic medications may be considered for people with FRDA displaying overactive bladder symptoms.	GPP
Intradetrusor injections of Botulinum toxin A or suprapubic catheterization may be considered as alternative intervention.	GPP
In a patient with persistently elevated post void residual volumes in excess of 100 mL, clean intermittent self-catheterization is indicated.	GPP

2.11 Bowel Dysfunction

Recommendations	Grading
Consider modifying diet and lifestyle to optimize stool consistency and avoid fecal incontinence.	GPP
Titrate appropriate laxatives to optimize gut transit, stool consistency and avoid fecal impaction. Consider the use of prokinetic drugs.	GPP
Avoid fecal incontinence by treating fecal impaction if present. Facilitate prompt rectal evacuation via use of manual manoeuvres, use of suppositories/mini enemas. Consider use of transanal irrigation and biofeedback behavioral therapy.	GPP

2.12 Sexual Function

Recommendations	Grading
Individuals with FRDA may benefit from discussion regarding their sexual function.	GPP
Reported sexual dysfunction should be investigated.	GPP
Symptomatic management of erectile dysfunction involves the use of phosphodiesterase-5 inhibitors but should only be prescribed in an individual with cardiac disease after consultation with the individual's cardiologist.	GPP

2.13 Audiological Function

Recommendations	Grading
People with FRDA should undergo a comprehensive auditory evaluation at the time of diagnosis and thereafter annually undertake a hearing screen or sooner if warranted by a sudden change in auditory performance.	B (28)
Instruction in "listening tactics" may be beneficial for individuals with hearing difficulties.	B (29)
FM-listening devices fitted by an audiologist may improve day-to-day listening and general communication in individuals with FRDA.	B (30)
Conventional hearing aids and cochlear implants may not improve the hearing impairment related to FRDA.	GPP

2.14 Cognition

Recommendations	Grade
Consideration should be given to changes in cognitive function that may impact on independence.	GPP
The impact of cognitive capacity on academic skills should be considered in academic environments.	GPP

2.15 Rehabilitation

Recommendations	Grade
Intensive inpatient rehabilitation is beneficial in improving function for people with FRDA.	C (14)
People with FRDA may require a cardiological opinion prior to undergoing aquatic physical therapy.	GPP
Rehabilitation may be provided in various home or community based settings.	GPP
Rehabilitation should be provided by allied health staff with expertise in neurological conditions.	GPP
People with FRDA may benefit from maintenance rehabilitation and regular review of function.	GPP

3.1 The Heart in Friedreich Ataxia

Recommendations	Grade
Cardiac evaluation and non-drug therapy	
An EKG and an echocardiogram should be performed at diagnosis and then at least annually.	GPP
A Holter and/or Loop monitor assessment should be performed if an individual with FRDA has palpitations.	GPP
Evaluation by a cardiologist should take place if an individual with FRDA has cardiac symptoms or abnormal results on cardiac testing.	GPP
Evaluation by a cardiologist should take place prior to major surgery.	GPP
Cardiac monitoring should take place during major surgery.	GPP
Major surgery should ideally be conducted in a center with cardiac intensive care facilities.	GPP
Exercise therapy including structured aerobic exercise and light weights, is recommended.	GPP
Heavy weight training is not advised.	GPP
Pharmacological therapy for slowing or prevention of deterioration of left ventricular contraction in asymptomatic individuals with reduced ejection fraction	
An angiotensin converting enzyme inhibitor (enalapril, ramipril, lisinopril or trandolapril) is first line therapy but if the angiotensin converting enzyme inhibitor is not tolerated then an angiotensin 2 receptor blocker (candesartan, valsartan) should be commenced instead (second line therapy).	C (31)
Beta blockers (carvedilol, bisoprolol or long acting metoprolol) should be considered as an addition to an angiotensin converting enzyme inhibitor or angiotensin 2 receptor blocker, particularly if the heart rate is >75/min.	GPP
Pharmacological therapy for treatment of symptomatic heart failure with reduced LV ejection fraction	
A diuretic should be prescribed for fluid overload.	C (31)

An angiotensin converting enzyme inhibitor (enalapril, ramipril, lisinopril or trandolapril) is first line therapy but if the angiotensin converting enzyme inhibitor is not tolerated then an angiotensin 2 receptor blocker (candesartan, valsartan) should be commenced instead (second line therapy).	C (31)
Beta blockers (carvedilol, bisoprolol or long acting metoprolol) should be added (first line therapy) to the angiotensin converting enzyme inhibitor or angiotensin 2 receptor blocker, however the role of beta blockers in children is less clear.	C (31)
Spironolactone or eplerenone should be prescribed for individuals with New York Heart Association (NYHA) stage 3 or 4 symptoms	C (31)
Calcium channel blockers with negative inotropic effects (verapamil and diltiazem) should be avoided.	C (31)
Digoxin should be prescribed for control of ventricular response if atrial fibrillation is present.	C (31)
Device therapy for subjects with symptomatic heart failure and reduced ejection fraction	
Implantation of an automatic internal cardioverter defibrillator should be considered if left ventricular ejection fraction (LVEF) is $\leq$ 35%, the individual has NYHA functional class 2 or 3 symptoms despite receiving optimal medical therapy, and the individual has a reasonable expectation of survival with good functional status for more than 1 year.	C (32)
Cardiac resynchronization therapy should be considered in individuals with LVEF of $\leq$ 35%, sinus rhythm, a QRS duration $\geq$ 0.12 seconds and NYHA functional class 3 or 4 symptoms despite receiving optimal medical therapy.	C (32)
Antiarrhythmic agents for prevention of recurrence of atrial arrhythmias	
Agents which can be considered for use in this setting are a beta blocker (metoprolol, bisoprolol or carvedilol), sotalol, dofetilide or amiodarone.	C (33)
Agents to be avoided include quinidine, flecainide, propafenone and disopyramide due to their negatively inotropic and/or pro-arrhythmic effects.	C (33)
Anticoagulation for atrial arrhythmias	
Anticoagulation should not be commenced if the LVEF is normal and there are no other risk factors for thromboembolism.	C (33)
Anticoagulation with warfarin or one of the novel anticoagulants (dabigatran, rivaroxaban or apixaban) should be considered in paroxysmal or permanent AF if one $CHADS_2$ risk factor is present and is generally indicated if more than one $CHADS_2$ risk factor is present.	C (33)
Anticoagulation with warfarin or one of the novel anticoagulants (dabigatran, rivaroxaban or apixaban) is strongly recommended in paroxysmal or permanent AF if there is reduced LVEF.	C (33)
Antiarrhythmic agents for prevention of recurrence of ventricular arrhythmias	

A beta blocker (metoprolol, bisoprolol or carvedilol) should be used, but sotalol and amiodarone are second-line options if there is arrhythmia recurrence despite beta blocker use.	C (32)
Cardiac Transplantation	
It is recommended that individuals with FRDA should be considered for heart transplantation if they experience severe heart failure which does not respond to maximal medical management.	GPP

3.2 Sleep

Recommendations	**Grading**
Clinicians, caregivers and individuals with FRDA should be aware there is increased prevalence of obstructive sleep apnea (OSA) as FRDA progresses.	C (34)
Annual evaluation of presence of sleep disordered breathing may be undertaken by administering of the Epworth Sleepiness Scale and reporting of clinical symptoms.	C (34)
For individuals with FRDA there should be a lower threshold for referral to a Sleep Physician and for polysomnography.	C (34)
Nasal continuous positive airway pressure therapy should be considered in the treatment of OSA.	C (35)

3.3 Pain Management and Anaesthesia

Recommendations	**Grading**
Consideration should be given to appropriate management of peri-operative pain in people with FRDA.	GPP
Consideration should be given to the use of nondepolarizing muscle relaxants, in particular accurate assessment of neuromuscular block throughout anesthesia.	D (36, 37)
Consideration should be given to avoiding risks associated with hyperkalemia.	GPP
There should be careful monitoring of fluid balance and cardiovascular function in people with FRDA undergoing anesthesia.	GPP

4. Scoliosis

Recommendations	**Grading**
Individuals with FRDA with a spinal curve between 20° and 40° and/or between the ages of 10-16 years should be observed for curve progression.	GPP
Bracing may not reduce or stop the progression of curves however may be valuable in delaying surgical correction in the young child.	D (38)
People with FRDA with a scoliosis >40° may be considered appropriate for surgical correction.	D (39, 40)
Consideration should be given to delaying surgical intervention in	D (38)

ambulant individuals with FRDA.	
All people with FRDA considered for scoliosis surgery require extensive pre-operative evaluation and planning regarding cardiac and pulmonary function.	GPP

5. Diabetes Mellitus

Recommendations	Grading
HbA1C may not be a good screening/diagnostic test in FRDA as it is not recommended in young individuals and in people in whom diabetes may present acutely.	GPP
Blood glucose should be measured at least once a year	GPP
Oral glucose tolerance tests have a better sensitivity than fasting plasma glucose or HbA1c to detect early changes in glucose metabolism, and enable earlier diagnosis of diabetes.	GPP
Diabetes treatment should be initiated early.	GPP
Lifestyle changes (diet and exercise) should be implemented in all with diabetes.	GPP
Insulin therapy should be initiated if diet and exercise alone do not achieve glucose control.	GPP

6. Genetic Issues

Recommendations	Grading
Any individual in whom the diagnosis of FRDA is considered should undergo testing for FRDA.	GPP
Referral to a clinical geneticist or genetic counselor should be considered on diagnosis of FRDA.	GPP
Requests for pre-symptomatic genetic testing are best managed on a case-by-case basis; there is no evidence to support the routine provision or refusal of pre-symptomatic genetic testing for FRDA.	GPP
The committee did not reach consensus on the issue of whether it is appropriate to conduct presymptomatic testing in a minor. Where a request for presymptomatic testing in a minor occurs, the individual/family should be referred to a team with expertise in this field for discussion about pre-symptomatic genetic testing in which the risks and benefits of pre-symptomatic genetic diagnosis are put forward. The risks and benefits from both the child's and parents' perspectives should be carefully reviewed during the pre-test assessment.	GPP
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, and if necessary a bioethicist, should be considered.	GPP
All patients identified pre-symptomatically and their families would benefit from immediate post-test counseling and psychosocial	GPP

support and referral for appropriate neurological and cardiac surveillance.	
Minors who have the maturity to do so, should be involved in the decision as to whether or not they are tested.	GPP
There is no evidence to support routine use of anti-oxidant therapies, such as idebenone in patients diagnosed pre-symptomatically.	GPP
Carrier testing should be first undertaken on the closest relative.	GPP

7. Friedreich ataxia due to compound heterozygosity for a *FXN* intron 1 GAA expansion and point mutation/ insertion/ deletion

Recommendation	Grading
If a person compound heterozygous for a *FXN* GAA expansion and a point mutation/deletion has a similar phenotype to those with FRDA due to homozygosity for GAA expansions, they should be managed as per the guidelines in this document.	GPP
If spastic ataxia is the predominant phenotype, then the main management issue is that of spasticity and the guidelines for management of spasticity should be followed.	GPP
It should never be assumed that other features of typical FRDA will not be present (e.g. cardiomyopathy, diabetes) and therefore monitoring for these should take place.	GPP

8. Pregnancy

Recommendations	Grading
The availability of testing for carrier status of reproductive partners should be made known to couples where one member has FRDA. If testing is requested, the carrier status of the unaffected partner should be established prior to conception in order to advise the couple of the risk of having a child with FRDA and to offer appropriate counseling.	GPP
When possible, it is advisable for women to have children earlier in their disease course.	GPP
Glucose tolerance testing should be performed between 24-28 weeks of gestation or earlier for individuals deemed to be at high risk by their practitioner.	D (41)
Women with FRDA should have close monitoring by a cardiologist during pregnancy.	GPP
Pregnant women with FRDA and deep venous thrombosis should be treated with Heparin as opposed to Warfarin	D (42)
Vaginal delivery can be expected for most pregnancies in women with FRDA.	D (43)
Close fetal monitoring during delivery is recommended.	D (44)
If Cesarean section is medically indicated, epidural or spinal anesthesia can generally be safely used in women with FRDA.	D (45, 46)

9.1 Quality of Life

Recommendations	Grading
Adherence to the guidelines for managing FRDA may improve quality of life.	GPP

9.2 Mental Health Issues

Recommendations	Grading
Individuals with FRDA require regular evaluation in terms of risks for developing depression and/or other mental health issues.	GPP
Individuals with FRDA may benefit from regular counseling to assist in adjusting to transitional events and possibly prevent the emergence of related depression.	GPP
Individuals with FRDA identified with depression should be treated with established interventions including counseling +/- pharmacological agents.	GPP
The risk of suicide in individuals with FRDA should be considered and managed proactively	GPP

9.3 Provision of Wheelchairs and Seating Systems

Recommendations	Grading
Prescription of a manual or powered wheelchair or scooter should be preceded by an assessment of the home/school/work and community environment the equipment will be used in.	GPP
A comprehensive prescription of a manual or powered wheelchair or scooter should be completed by a qualified clinician familiar with the specific issues related to FRDA.	GPP
A validated assessment and evaluation tool for wheelchair and seating prescription may be used to guide the process of prescription and evaluation.	GPP
In prescribing a manual wheelchair and seating system, functional capacity should not be impeded for the sake of an anatomically correct seated posture.	GPP
Appropriate training should be provided regarding the safe use of the wheelchair or scooter in the home or community environment.	GPP
Suitability of the seating and wheelchair system should be evaluated on an annual basis in adults and bi-annually in children.	GPP

9.4 Independence Issues

Recommendations	Grading
Individuals with FRDA may benefit from a detailed assessment identifying barriers to independence.	GPP

Compensatory or remedial intervention may improve independence in individuals with FRDA.	GPP

9.5 Advance Care Planning and End of Life Care

Recommendations	Grading
Professionals should facilitate advance care planning and documentation of advance care directives in individuals with FRDA.	GPP
Advance care directives documented for individuals with FRDA should be regularly reviewed by the individual in conjunction with their treating clinicians.	GPP

9.6 Palliative Care

Recommendations	Grading
Neurology, rehabilitation and palliative care services should develop closely coordinated working links to support people with FRDA from diagnosis to death, including: • proper flow of communication and information for patients and their families • A designated point of contact for each stage in the pathway.	GPP
Individuals with FRDA and a limited lifespan (for example, likely to die within 12 months) and/or distressing symptoms, and/or a need for end-of-life planning generally benefit from a referral to a palliative care team.	GPP
An individual identified as dying from FRDA may benefit from ongoing access to palliative care services including symptom and pain control, psychological and spiritual support and specialist input if needed.	GPP

9.7 Potential Medications/Compounds for Use in Friedreich Ataxia

Recommendations	Grading
As there are no proven treatments that alter natural history it is not recommended that any pharmaceutical agent be routinely prescribed to individuals with FRDA.	A (47-50)
Idebenone is the most studied pharmacological agent in FRDA. Studies to date indicate the use of Idebenone in individuals with FRDA does not result in significant changes to neurological or cardiac status over an extended period of time.	A (47, 49-56)

Glossary/Abbreviations

ABR: Auditory Brainstem Response
ACP: Advanced Care Planning
ADRT: Advance Decision to Refuse Treatment
AFO: Ankle Foot Orthosis
AHI: Apnea-Hypopnea Index
APGAR: Appearance, Pulse, Grimace, Activity, Respiration
AVED: Ataxia with Vitamin E Deficiency
BDI: Beck Depression Inventory
CAGRS: Cooperative Ataxia Group Rating Scale
CCRN: Collaborative Clinical Research Network
CD: Cotrel-Dobousset
CEPO: Carbamilated Erythropoietin
CISC: Clean Intermittent Self-Catheterization
CP: Cerebral Palsy
CSA: Central Sleep Apnea
CVS: Chorionic Villus Sampling
DBPCC: Double Blinded Placebo Controlled, Crossover trial
DNA: Deoxyribonucleic Acid
DRG: Dorsal Root Ganglion
DVT: Deep Vein Thrombosis
EKG: Electrocardiography
EDS: Excessive Daytime Sleepiness
EMG: Electromyography
EPO: Erythropoietin
ESS: Epworth Sleepiness Scale
FAIS: Friedreich Ataxia Impact Scale
FARR: Friedreich Ataxia with Retained Reflexes
FARS: Friedreich Ataxia Rating Scale
FBC: Full Blood Count
FIM: Functional Independence Measure
FRDA: Friedreich Ataxia
FXN: Frataxin
GAA: Guanine-Adenine-Adenine
HDAC: Histone Deacetylase
IAPS: Inherited Ataxia Progression Scale
ICARS: International Cooperative Ataxia Rating Scale
ICU: Intensive Care Unit
IPA: Indole-3-Propionic Acid
IVF: In Vitro Fertilization
LHON: Leber Hereditary Optic Neuropathy
LOFA: Late Onset Friedreich Ataxia
LSVT: Lee Silverman Voice Technique
MAS: Mandibular Advancement Splint
MBI: Modified Barthel Index

MDT: Multidisciplinary Team
MMPI: Minnesota Multiphasic Personality Inventory
MRI: Magnetic Resonance Imaging
MRS: Magnetic Resonance Spectroscopy
MS: Multiple Sclerosis
NADPH: Nicotinamide Adenine Dinucleotide Phosphate
NICU: Neonatal Intensive Care Unit
NIRS: Near Infrared Muscle Spectroscopy
NSFLTNC: National Service Framework for Long Term Neurological Conditions
OAE: Otoacoustic Emissions
OCT: Optical Coherence Tomography
OSA: Obstructive Sleep Apnea
QOL: Quality of Life
PGD: Preimplantation Genetic Diagnosis
PSG: Polysomnography
RDBPCT: Randomized Double Blinded Placebo Controlled Trial
RLS: Restless Leg Syndrome
RNA: Ribonucleic Acid
RT: Reaction Time
SARA: The scale for the assessment and rating of ataxia
SDB: Sleep Disordered Breathing
SLP: Speech and Language Pathologist
ST-T: Spinothalamic Tract
TFT: Thyroid Function Test
UMN: Upper Motor Neuron
UTI: Urinary Tract Infection
VLOFA: Very Late Onset Friedreich Ataxia
WHO: World Health Organization

1 Overview of Friedreich ataxia

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First submitted: 10/08/2012

1.1 Clinical Features of Friedreich ataxia

The variable susceptibility of different components of the neuroaxis and somatic organs to deficient frataxin leads to the distinct range of clinical manifestations of Friedreich ataxia (FRDA), which includes mixed upper and lower motor neuron signs and extra-neurologic manifestations.

Mean age of symptom onset in FRDA is 10 to 15 years (57-59). Whilst the large majority of individuals present with gait ataxia, less typical presenting neurologic symptoms include spastic paraparesis, sensory neuropathy, tremor, dysarthria, and chorea (57, 60-62). Some individuals present with scoliosis or cardiomyopathy, which can predate the onset of neurologic symptoms by a number of years, leading to a delay in diagnosis (57, 59, 60).

The cardinal features of FRDA are highlighted by the diagnostic criteria proposed prior to discovery of the *FXN* gene, first by Geoffroy and colleagues (63), and refined by Harding (58) (Table 1). These include progressive gait and limb ataxia, lower limb areflexia, extensor plantar responses, and dysarthria. Decreased posterior column function (manifest as decreased vibration sensation and proprioception) and lower limb weakness are also typical. Whilst almost all individuals with FRDA have ataxia and lower limb areflexia at presentation, dysarthria and posterior column dysfunction may not develop until some years after disease onset (58). Lower limb reflexes are also preserved in some individuals (10-15%). This initially led to the description of a separate clinical phenotype 'Friedreich ataxia with retained reflexes', however it has become evident that this is a variation of classic FRDA (59, 64).

Harding's diagnostic criteria also stipulated an onset age of less than 25 years, and whilst the majority do present within this time-frame, genetic testing has confirmed that later onset does occur (late onset Friedreich ataxia, LOFA, onset >25 years; very late onset Friedreich ataxia, onset >40 years), (59) with the latest onset reported in the literature being 64 years of age (65).

Pyramidal lower limb weakness worsens with disease progression in the majority of individuals (58). Untreated, spasticity can lead to contractures and painful muscle spasms. Whilst the peripheral neuropathy of FRDA is described to be predominantly sensory, some individuals also have evidence of a motor neuropathy, with distal weakness and wasting, and neurogenic findings on electromyography (66, 67). The involvement of unmyelinated sensory and autonomic nerve fibers is probably also responsible for the cold and cyanosed extremities experienced by almost all individuals with FRDA (68-70). Neurogenic bladder symptoms occur in up to 50% of individuals (57, 71). Orthopedic complications include scoliosis (which occurs in 60 to 80%), and pes cavus (in up to 80% of individuals) (57, 59, 72). Back pain is a common complaint, due to a combination of paraspinal muscle spasm, spinal deformity, and poor seating/posture in those who are wheelchair dependent.

Optic atrophy and/or visual impairment are reported in 5 to 25% of individuals with FRDA (58, 59, 71). Subclinical optic nerve involvement, however, is present in most other individuals, demonstrated by abnormalities on visual evoked potential testing and optical coherence tomography (73). Eye movement abnormalities are very common, particularly fixation instability with square wave jerks (present in up to 90% of individuals) (69, 71). Nystagmus occurs in up to 40% (59). Some individuals complain of oscillopsia (74). Whilst hearing loss, defined as impaired sound detection, is present in only 10% of individuals, auditory neuropathy, manifest as impaired auditory temporal processing and difficulties with speech understanding in background noise, is very common (75, 76). Dysphagia tends to occur later in the disease course (59).

Cardiac involvement is an important feature of FRDA. Not only is its presence a diagnostic clue in a person presenting with progressive ataxia,(77) but it is the most common cause of early mortality. Echocardiographic evidence of hypertrophic cardiomyopathy is apparent in 60-70% of individuals, however many are asymptomatic, particularly early in the disease course (57, 59, 78). In the later stages, cardiac failure may occur. Arrhythmias, particularly atrial arrhythmias may occur (71, 72). ECG abnormalities are present in 80 to 90% of individuals. ST-T wave abnormalities are the most common finding (68, 79). Diabetes mellitus occurs in 10 to 15% of individuals (58, 80).

The progression of disease in FRDA is variable. The mean time to wheelchair dependency from symptom onset is 10 to 15 years (57-59). Whilst the mean life expectancy of FRDA is reported to be only 36.5 years in the published literature (cardiac dysfunction including congestive heart failure and arrhythmia being the leading cause of death) (58, 81, 82) improved medical care, the identification of later onset, and less severe phenotypes with genetic testing have resulted in an improvement in not only survival, but also quality of life (83).

1.2 Genetics and pathophysiology of Friedreich ataxia

FRDA has an estimated incidence of 1 in 29 000 and carrier frequency of 1 in 85 individuals of Caucasian background (84). It is thought that most expanded alleles derive from a common founder (84).

FRDA is due mutations in *FXN*, located on chromosome 9q, which encodes a 210 amino acid protein named frataxin. Homozygosity for a GAA triplet repeat expansion in intron 1 of *FXN* occurs in 96-98% of individuals with FRDA. The remainder of individuals are heterozygous for the triplet repeat expansion and a point mutation or deletion (85-87). FRDA is associated with alleles containing 66 to 1300 GAA triplet repeats, with most expanded alleles containing between 700 to 1000 repeats (59, 69, 85). Normal alleles contain up to 33 repeats (84, 88).

Individuals with FRDA have a marked deficiency of *FXN* mRNA and frataxin (89, 90). The expanded GAA repeat is thought to interfere with *FXN* transcription in a length-dependent manner by forming abnormal DNA conformations such as triplexes, which self-associate to form structures called ‘sticky DNA’.

Frataxin is a mitochondrial protein (90-92) with high levels of expression in the heart, skeletal muscle, spinal cord, and cerebellum (85, 90). It is thought to play a role in iron-sulfur cluster synthesis and mitochondrial iron homeostasis. Deficiency of frataxin leads to deficiencies of iron-sulfur cluster containing respiratory chain complexes I to III, and aconitases,(93, 94) which results in impaired mitochondrial respiratory chain function, (91) and mitochondrial iron accumulation (57, 95). In addition, cells lacking frataxin exhibit increased sensitivity to oxidative stress (96). DNA methylation upstream of the GAA expansion has also been shown to correlate with expression of *FXN* (97).

1.3 Genotype phenotype correlations

The variability in symptom onset, severity and progression of disease seen in FRDA can be partly explained by the size of the triplet repeat expansion, particularly of the smaller allele (GAA1). GAA1 size also correlates inversely with frataxin protein expression (89). The size of the larger allele (GAA2) contributes less to the clinical phenotype (57, 59).

Numerous groups have demonstrated that the size of the GAA1 allele correlates with age at symptom onset, age of wheelchair dependency, and time from symptom onset to wheelchair dependency (57, 59, 88). Nearly 50% of the variability of age at onset is thought to be explained by GAA1 size (80). However, for individuals with GAA1 sizes of 700 to 900 repeats, GAA1 is a poor predictor of age at onset (80, 98).

Age at symptom onset also correlates with rate of disease progression (88). GAA1 size also correlates with the presence of cardiomyopathy and scoliosis in some cohorts (57, 59, 80). Other clinical features such as dysarthria, decreased vibration sensation, dysphagia and sphincter disturbance correlate more with disease duration than GAA1 size (57, 59, 99).

1.4 Atypical Friedreich ataxia phenotypes

Up to 25% of individuals who are homozygous for the GAA triplet repeat expansion in *FXN* can be classified as having 'atypical' FRDA due to variations from the 'classical' FRDA phenotype (58). These phenotypes include late onset FRDA (LOFA) where onset is after 25 years of age; very late onset FRDA (VLOFA) where onset is after 40 years, and FRDA with retained reflexes (FARR) (59, 60, 88, 100). These phenotypes are however, arbitrary in nature, and better thought of as a spectrum of disease severity and clinical manifestations of the same genetic disorder, rather than being separate entities. The size of the GAA1 allele accounts for some of these differences, particularly age at onset. Individuals with FARR generally have a typical course and similar GAA1 size to classic FRDA although some have later disease onset (60, 88).

FRDA in the Acadian population varies from the typical FRDA phenotype in that despite having similar GAA1 sizes to classical FRDA, these individuals have later age at onset, and slower disease progression. Cardiomyopathy is also less common in this population (88). Some individuals with particular point mutations also have an atypical phenotype (see section 7). For example, those compound heterozygous for the G130V mutation and a GAA

expansion often present with spastic paraparesis, minimal cerebellar ataxia and dysarthria, and have a slowly progressive course (101, 102).

1.5 Differential diagnosis

An individual with a chronic progressive ataxia presents a diagnostic challenge. The differential diagnosis is broad, causative conditions are individually uncommon, and some of the clinical features overlap. Determining the mode of inheritance is important if possible. In most populations, FRDA is the most common autosomal recessive ataxia (103). The presence of cardiomyopathy is a useful diagnostic clue for diagnosis of FRDA (77).

Table 2 lists some of the differential diagnoses of FRDA; detailed descriptions of these conditions should be sought elsewhere. Age of onset and characteristic clinical and MRI features, including the presence/absence of early cerebellar atrophy are provided. Significant cerebellar atrophy is usually not seen in FRDA (69) and its presence should lead to consideration of alternate diagnoses. Ataxia and/or cerebellar signs are a prominent feature of most of the conditions listed; some treatable conditions that occasionally present with cerebellar signs are also listed (e.g. Wilson disease). Charcot-Marie-Tooth disease, a heterogeneous group of inherited sensorimotor neuropathies is listed as a differential diagnosis for individuals with FRDA that present with a prominent peripheral neuropathy with pes cavus. For individuals who present with a spastic paraparesis, the hereditary spastic paraplegias should be considered as the main differential diagnosis.

Ataxia with vitamin E deficiency (AVED) due to mutations in *TTPA* (which encodes α-tocopherol transfer protein) presents with a very similar phenotype to FRDA (104). Vitamin E deficiency, which may also be due to disorders causing fat malabsorption such as abetalipoproteinaemia, (105) is important to diagnose, as it is treatable with lifelong Vitamin E supplementation (106). Onset of AVED is usually in the first two decades of life. Clinical features include progressive ataxia, dysarthria, dorsal column dysfunction, areflexia, and upgoing plantar responses. Cardiomyopathy occurs in some patients but is uncommon. Decreased visual acuity and head titubation are more frequent in AVED than FRDA. Serum vitamin E concentrations are low (107, 108).

Table 1 Diagnostic criteria for Friedreich ataxia proposed by Geoffroy and colleagues (1976) and Harding (1981)

Criteria	Geoffroy et. al., (1976)	Harding (1981)
Primary	1. Onset before end of puberty (never after age 20 years) 2. Progressive ataxia of gait 3. Dysarthria 4. Loss of joint position or vibration sense 5. Absent tendon reflexes 6. Muscle weakness	1. Onset before age 25 years 2. Progressive unremitting ataxia of limbs and gait 3. Absent knee and ankle jerks

Secondary	1. Extensor plantar responses 2. Pes cavus 3. Scoliosis 4. Cardiomyopathy	1. Dysarthria 2. Extensor plantar responses
Supportive	-	If secondary criteria absent, require: 1. Affected sib fulfilling primary and secondary criteria 2. Median motor nerve conduction velocities > 40 m/s (excluding HMSN type 1*)

*Now referred to as Charcot-Marie-Tooth disease type 1

Table 2 Summary of differential diagnoses for Friedreich ataxia

Condition	Inheritance	Onset age	DD/ID	PN	Other movt dsd	Ophthalmologic abnormalities	Other clinical features	Early cerebellar atrophy	Other MRI features	Diagnostic tests
AVED	AR	Late childhood, adolescence	-	+	+/-	↓ acuity, retinitis pigmentosa	Prominent post column loss. Pyramidal signs. Cardiomyopathy	-	-	↓vitamin E, *TTPA* genetic testing
AT	AR	Early childhood	-	+/-	+	Oculomotorapraxia	Telangiectasia, immunodeficiency	-	-	↑AFP, low Igs, *ATM* genetic testing
AOA1	AR	Childhood	+/-	+	+	Oculomotorapraxia	Hypoalbuminaemia, hypercholesterolaemia	+	-	*APTX* genetic testing
AOA2	AR	Late childhood to early adulthood	-	+	+	Oculomotorapraxia	Moderately elevated AFP. Raised CK in some	+	-	*SETX* genetic testing
ARSACS	AR	Childhood	-	+	-	-	Marked spasticity. Hypermyelinated retinal fibres	+	Linear pontine hypointensities	*SACS* genetic testing
CTX	AR	Childhood-adulthood	+	+	+/-	Cataracts	Tendon xanthomas, chronic diarrhoea, seizures	+	Cerebral atrophy, WM abnormalities	↑cholestanol. *CYP27A1* genetic testing
Marinesco-Sjogren syndrome	AR	Childhood	+	-	-	Cataracts	Myopathy, hypogonadism, short stature, skeletal anomalies	+	Cerebellar cortical T2 abnormalities	Electron dense structures on muscle biopsy. *SIL1* genetic testing
SCAN1	AR	Adolescence	-	+	-	-	Hypoalbuminaemia, hypercholesterolaemia	+	-	*TDP1* genetic testing
CACNA1A related disorders	AD	Early and late childhood	+/-	-	-	Nystagmus	Seizures, stroke-like episodes, hemiparesis	+	-	*CACNA1A* genetic testing
SCAs	AD	Often adulthood,	-	+/-	+/-	+/-	Phenotypic variability	+	Spinal cord	Specific genetic testing

		but also childhood								
GAN	AR	Early to mid childhood	+	+	-	-	Kinky hair, pyramidal signs	-	WM signal abnormalities	Giant axons on nerve biopsy. *GAN* genetic testing
CMT	Variable	Childhood to adulthood	-	+	-	-		-	-	Specific genetic testing
Metabolic disorders										
Mitochondrial disorders	Variable	Wide range	+/-	+/-	+/-	+/-	Variable	+/-	Variable brainstem, basal ganglia and WM abnormalities	Lactate/pyruvate abnormalities, muscle respiratory chain analysis, genetic testing of mtDNA/ nuclear DNA
CoQ10 deficiency	AR	Childhood to adulthood	+	+	-	+/-	Seizures, myopathy, pyramidal signs	+	-	CoQ10 deficiency in muscle/fibroblasts, genetic testing (various genes)
Late-onset GM2 gangliosidosis	AR	Childhood to adulthood	-	-	+	Optic atrophy, retinitis pigmentosa	Seizures, cognitive regression, psychiatric disturbance	+	-	Beta-hexosaminidase A enzymatic testing, *HEXA* genetic testing
Abetaliproteinaemia	AR	Infancy and childhood	-	+	-	Retinitis pigmentosa	Diarrhoea, fat malabsorption (including Vitamin E deficienc), red cell acanthocytosis	-	-	Extremely low cholesterol levels, abnormal lipoprotein profile. *MTP* genetic testing
Refsum disease	AR	Childhood to young adulthood	-	+	-	Retinitis pigmentosa	Deafness, anosmia, ichthyosis	-	-	↑Phytanic acid, deficiency of PhyH enzyme activity. Genetic testing of *PHYH*, *PEX7*.
CDG1a	AR	Infancy to adulthood	+/-	+	+	+/-	Seizures, hypogonadism,	+	White matter abnormalities	Abnormal transferrin isoform pattern.

							skeletal abnormalities			Deficient phosphomannomutase activity, *PMM2* genetic testing
Wilson disease	AR	Childhood to adulthood	-	-	+	Kayser-Fleischer rings	Liver disease, psychiatric disturbance	-	Basal ganglia, thalamic and brainstem abnormalities	↓serum copper and caeruloplasmin, ↑urinary copper excretion, *ATP7B* genetic testing

Abbreviations:
AD = autosomal dominant; AFP = alpha-fetoprotein; AOA1/2 = Ataxia with oculomotor apraxia 1/2; AR = autosomal recessive; ARSACS= Autosomal recessive spastic ataxia of Charlevoix-Saguenay; AT = Ataxia telangiectasia; AVED = Ataxia with vitamin E deficiency; CDG1a = Congenital disorder of glycosylation 1a; CK = creatine kinase; CMT = Charcot-Marie-Tooth disease; CTX = Cerebrotendinous xanthomatosis; DD/ID = significant developmental delay/ intellectual disability; GAN = Giant axonal neuropathy; PhyH = phytanoyl-CoA hydroxylase; PN = peripheral neuropathy; SCAs = Spinocerebellar ataxias; SCAN = Spinocerebellar ataxia with axonal neuropathy; WM = White matter.

2. The neurological components of Friedreich ataxia

2.1 Ataxia

Author: Dr Andrew McGarry

2.1.1 Overview

Ataxia, defined as the decomposition of voluntary movement, is the clinical hallmark of Friedreich ataxia (FRDA). Indeed, Harding indicated progressive ataxia of gait and all limbs was an essential diagnostic criterion for FRDA (58). The irregular, uncoordinated movements of FRDA are reflective of dysfunction of proprioceptive systems, the cerebellum (particularly the deep nuclei), corticospinal tracts, visual and vestibular systems, and musculoskeletal structures. These changes progressively accumulate and collectively worsen the execution of smooth limb movements and gait, accounting for substantial disability. The ataxia related to FRDA has been described as both afferent (as a result of proprioceptive dysfunction) and efferent (as a result of cerebellar pathology). Ataxia appears to affect many motor pathways as evident in hand function by dysmetria, dysdiadochokinesia and intention tremor; speech and swallowing by dysarthria and generally in the latter stages of the disease, dysphagia; and vision in terms of instability of fixation with square wave jerks. As such, ataxia represents a major impediment for activities of daily living and quality of life.

Ataxia, in the majority of individuals with FRDA is typically noticed in early childhood or adolescence, manifesting as clumsiness and falls. While there is some variability in the severity of ataxia based on genotype and age of onset, ataxia universally precipitates dysfunction at some point in the natural history of FRDA.

2.1.2 Review of Literature for Treatment of Ataxia Interventions in Friedreich ataxia: Pharmacologic

To date, several compounds have been evaluated in open-label and randomized, blinded, placebo controlled trials for their effect on ataxia. In particular, idebenone, deferiprone, erythropoetin, EPI 743 and EPI A0001 have been evaluated (see Table 3). While numerous statically insignificant observations have suggested improvement, and sub-analyses in some smaller trials have been significant, no drug tested in a large trial has yet demonstrated a consistent, robust improvement in ataxia.

2.1.3 Review of Literature for Treatment of Ataxia in Friedreich ataxia: Non-pharmacologic

There are no clinical trials specifically establishing the efficacy of non-pharmacological methods of treatment, or comparing different methods to one another. Non-

pharmacologic efforts to improve ataxia emphasize physical therapy for maintenance of balance, flexibility and muscular strength, treatment of spasticity with medications or botulinum toxin, and optimization of orthopedic stability (foot deformities, scoliosis) with evaluations by orthopedists and podiatrists. Visual function, vestibular function, and proprioception can influence gait stability and coordination in FRDA, as in all ataxic disorders, and warrant surveillance by a neurologist to implement timely strategies for maximal safety and independence. Routine neurological evaluation also offers the advantage of allowing consideration of additional factors that may be unrelated to FRDA but can influence ataxia. Medical management of elements of FRDA such as glucose intolerance/diabetes and cardiovascular health is also essential towards maximizing the benefit of physical therapy and correctly tailoring interventions to the needs of an individual with FRDA. Occupational therapy is useful to evaluate potential physical risks in the living spaces of people with FRDA. Ultimately, clinical trials are needed to determine the most effective non-pharmacological methods to manage ataxia in people with FRDA.

2.1.4 Recommendations

Recommendations	**Grading**
Regular neurological examination should take place, and may guide referral to appropriate specialists in a timely fashion.	GPP
Physical therapy may be useful to help with balance, flexibility, accuracy of limb movements, and maintenance of strength.	GPP
Occupational therapy may identify risks for people with ataxia as well as help minimize difficulties in the performance of daily activities.	GPP
Routine orthopedic care is necessary to follow and treat orthopedic issues that can influence ataxia.	GPP

Table 3: Compounds shown to have an effect on ataxia in Friedreich ataxia as evaluated in open-label and randomized, blinded, placebo controlled trials.

Author/Sponsor/Year	Compound	Trial Design	Cohort Size	Dose	Duration	Ataxia measure	Effect on ataxia
Hausse et al, 2002 (51)	Idebenone	Open label	38	5mg/kg/day	6 months	Clinical evaluation	Subjective improvement
Artuch et al, 2002 (52)	Idebenone	Open label	9	5mg/kg/day	12 months	ICARS	Improvement in ICARS
Di Prospero et al, 2007 (53)	Idebenone	RDBPCT	48	180-2250mg/day based on body weight, divided into low, intermediate, high doses	6 months	ICARS/FARS	Improvement in ICARS and FARS in ambulatory subgroup on intermediate and high dose.
Pineda et al, 2008 (109)	Idebenone	Open label	24	5-20mg/kg/day	Up to 5 years	ICARS	Initial improvement in children, though back to base level after 5 years. No change in adults.
Lynch et al, 2010 (54) (IONIA-E)	Idebenone	Open label extension	68	1350-2250mg/day	12 months	ICARS/FARS	12 month: None. 18 months (data combined with IONIA) significant improvement in ICARS
Valasco-Sanchez et al, 2011 (55)	Idebenone Deferiprone	Open label	20	20/mg/kg/day for both Idebenone and	11 months	ICARS	No total change in ICARS though some change in

				Deferiprone			kinetic subscores
Boesch et al, 2008 (56)	Erythropoetin	Open label	8	2000IU 3x/week	6 months	SARA/FARS	Significant change in FARS/SARA.
Enns et al, 2012 (49)	EPI 743	Open label	1	50 mg/twice daily for 14 days then 100mg/twice daily to day 29 when increased to 100mg/thrice daily.	444 days	Scale not used	Some clinical improvement in strength, speech and vision
Lynch et al, 2012 (47)	EPI AOO01	RDBPCT	31	Placebo, low (510mg) and high dose (750 mg)	28 days	FARS	Significant improvement in both groups

Legend
RDBPCT: Randomized double blinded placebo controlled trial
DBPCC: Double blinded placebo controlled, crossover trial
ICARS: International cooperative ataxia rating scale
CAGRS: Cooperative ataxia group rating scale
FARS: Friedreich ataxia rating scale
SARA: Scale for the assessment and rating of ataxia

2.2 Weakness

Author: Professor Massimo Pandolfo

2.2.1 Overview

There is ample clinical, pathological and neurophysiological evidence of motor system involvement in FRDA. Neuropathology (reviewed by (110)) reveals severe involvement of the pyramidal tracts. Myelin and axon loss in the corticospinal tracts is prominent and may even be visible to the naked eye. The distal portion of the pyramidal tracts is more severely affected, indicating a primary axonal, dying back pathology. Neurophysiological studies (111, 112) have shown slowing of central motor conduction time (CMCT) and reduction in motor evoked potentials (MEPs) that correlate with disease duration. These findings provide a pathological and pathophysiological substrate for the clinical observation of progressive weakness of central origin in FRDA, which affects the lower limbs more severely and earlier in the course of the disease. Conversely, there is little evidence of a primary lower motor neuron or peripheral nerve contribution to weakness. There is no significant motor neuron loss in the spinal cord, and ventral roots contain a normal number of myelinated fibers of normal size distribution (110, 113). Clinically, some distal amyotrophy occurs early in the disease in only a minority of patients, as noted in the classical 1981 description by Harding (58).

2.2.2 Review of the literature related to weakness in Friedreich ataxia.

Individuals with FRDA do not have clear cut clinical or pathological evidence of myopathy, however they often complain of fatigue (114, 115) and metabolic studies on muscle revealed abnormalities. The clearest evidence of a deficit of energy production comes from phosphorus magnetic resonance spectroscopy (MRS) studies. In 1999, Lodi and colleagues (116) "demonstrated a maximum rate of muscle mitochondrial ATP production (V(max)) below the normal range in all 12 individuals with FRDA and a strong negative correlation between mitochondrial V(max) and the number of GAA repeats in the smaller allele". These results were subsequently replicated by the same authors (117, 118) and by others (119). Lynch and colleagues (120) used "noninvasive continuous near infrared muscle spectroscopy (NIRS) to investigate the delivery and utilization of oxygen in response to exercise in this disorder. Participants performed an incremental treadmill walking protocol in which levels of muscle deoxygenation or oxygenation were continuously measured in the medial calf muscle. The kinetics of recovery from exercise-induced deoxygenation, called the half-time of recovery (t(1/2)) were determined. The t(1/2) was prolonged in individuals with FRDA compared with controls, and the degree of prolongation correlated with the length of the shorter GAA repeat, a genetic measure that correlates with the age of onset of disease. The t(1/2) also correlated inversely with participant age and with the maximum treadmill speed attained". These findings are also supported by the identification of an abnormal gene expression profile in skeletal muscle of partially frataxin-deficient mice, showing down regulation of genes expressed in aerobic slow fibers and of mitochondrial genes (121).

A systematic literature search only identified two studies specifically aimed at evaluating the impact of weakness in FRDA (59, 122). Most retrieved references were review articles, case reports or descriptions of small case series with prominent weakness and spasticity and little ataxia (123-131).

A recent clinical study explored whether muscle weakness has an impact on ataxia assessment by the International Cooperative Ataxia Rating Scale (ICARS) (122). The authors tested 12 children with FRDA (10 males, two females; mean age 13y 6mo, SD 2y 6mo) and 12 age-matched children without FRDA (nine males; three females). The authors found "significant muscle weakness in children with FRDA, more pronounced in proximal than in distal muscles (-2SD vs -0.5SD respectively; p=0.004) and with greater impairment of leg muscles than of arm muscles (-2SD vs -0. SD respectively; p=0.001)". Muscle ultrasound density "was homogeneously increased in the biceps, quadriceps, and tibialis anterior muscles (median 4SD) in children with FRDA", suggesting subclinical myopathy. The authors concluded that in children with FRDA, ataxia scales based on ICARS are confounded by muscle weakness.

An older study, preceding the availability of molecular diagnosis for FRDA, reviewed 170 muscular assessments in 33 individuals with FRDA between 1979 and 1992 (59) The authors could "delineate a fairly regular and statistically significant pattern of slowly progressive and symmetrical loss of strength affecting mainly the lower limbs, and more specifically the pelvic girdle muscles. The first significant weakness was observed in the hip extensor group, followed in a variable fashion by other muscle groups of the lower limb. Upper limb and trunk muscles remained relatively spared until late in the disease process, with an overall strength approximately 80% of normal. Use of a wheelchair began at a mean age of 18.2 years, at which time the lower-limb strength averaged 70% of normal. Patients became totally unable to walk at a mean age of 20.5 years old, with a further decline in lower limb strength to 56% of normal".

Iron deficiency may also contribute to fatigue and weakness in people with FRDA. Anemia increases fatigue, weakness, palpitations and shortness of breath. In addition there is some evidence that iron depletion may down regulate frataxin (132). Iron deficiency should be treated in people with FRDA.

2.2.3 Conclusion

Current data support the concept that weakness contributes to motor impairment in FRDA. Easy fatigability is a common complaint, probably related to inefficient energy production in muscle with subclinical myopathy. Weakness of central origin is progressive and becomes severe with advanced disease, significantly adding to the motor impairment caused by ataxia. Muscle atrophy, not very common in the early stages, becomes evident with advanced disease, possibly because of the primary metabolic abnormalities in muscle in addition to disuse. (See also Section 2.3)

2.2.4 Overview of recommendations

Non-pharmacologic treatment: Physical therapy and aerobic training are thought to lessen fatigue, improve strength and well-being, but evidence in the case of FRDA is weak. One study provided evidence that coordinative training improves motor performance and reduces ataxia symptoms particularly in patients with primary cerebellar ataxia, less in patients with afferent ataxia (three FRDA subjects were classified in the latter category). The endpoints of this study did not include specific strength or fatigue measures, but some of the motor performances that were evaluated can be affected by weakness (133).

Pharmacologic treatment: Treatments aimed at the improvement of mitochondrial function could in principle increase strength and lessen fatigue in individuals with FRDA.

A possible benefit of Idebenone is essentially based on anecdotal data and descriptive, open-label studies. However, the only randomized controlled trial (RCT) that evaluated changes in exercise capacity of children with FRDA (N=48; age range, 9-17 y) treated for six months with one of three doses of Idebenone (approximately 5, 15, and 45 mg/kg) or placebo failed to reveal any benefit (134). The main outcome measure in this study was “peak oxygen consumption per unit time (peak VO(2)) and peak work rate (WR) ... during incremental exercise testing at baseline and after treatment”. The authors concluded that “exercise capacity in children and adolescents with FRDA was significantly impaired. The basis for the impairment appears to be multifactorial and correlated to the degree of neurologic impairment. Although idebenone has previously been shown potentially to improve features of FRDA, idebenone treatment did not increase exercise capacity relative to placebo”.

Open-label treatment of 10 individuals with FRDA with 2,100 IU Vitamin E per day and 400 mg Coenzyme Q10 per day for 6 months resulted in an improvement in cardiac and skeletal muscle bioenergetics, as measured by 31P-magnetic resonance spectroscopy. This improvement was maintained throughout a 47-month period when the treatment was continued (117, 135). These studies, however, did not evaluate muscular strength or fatigue as outcome measures. Furthermore, the first study did not reveal any neurological improvement after six months and the second study concluded that “comparison with cross-sectional data from 77 individuals with FRDA indicated the changes in total International Cooperative Ataxia Rating Scale and kinetic scores over the trial period were better than predicted for 7 participants, but the posture and gait and hand dexterity scores progressed as predicted”.

A triple-phase crossover trial of L-carnitine (3 g/d) and Creatine (6.75 g/d) in 16 people with FRDA (136) had as “primary outcome measures ... mitochondrial ATP production measured as phosphocreatine recovery by Phosphorus magnetic resonance spectroscopy, neurological deficits assessed by the international co-operative ataxia rating scale and cardiac hypertrophy in echocardiography. After 4 months on L-carnitine phosphocreatine recovery was improved compared to baseline ($p<0.03$, t-test) but comparison to placebo and creatine effects did not

reach significance (p=0.06, F-test). Ataxia rating scale and echocardiographic parameters remained unchanged".

An RCT with L-acetylcarnitine (2 g per day) in 15 FRDA patients produced mild improvement of coordination after 3 months and 6 months. Again, strength and fatigue were not among the chosen outcome measures (137).

Several drugs have been tested for a possible benefit in reducing fatigue in other conditions. These include Amantadine, Fluoxetine, Modafinil, Armodafinil, Methylphenidate, Amphetamine and Dextroamphetamine composite, Fampridine (3-4 diaminopyridine). There are no data on any effect of these medications in FRDA.

2.2.5 Future studies

The prevalence, severity and clinical relevance of weakness and fatigue in FRDA indicate the importance of including appropriate outcome measures in future trials of pharmacological and non-pharmacological treatments. While bioenergetic parameters are useful to orient subsequent studies and to test mechanistic hypotheses, clinical and quality-of-life measures are essential to assess the potential benefit of any treatment aimed to relieve weakness and fatigue in FRDA.

Further research is required in the management of weakness and fatigue in FRDA.

2.2.6 Recommendations

Recommendations	Grading
Assessment of muscle weakness is an essential part of the functional evaluation of an individual with FRDA.	GPP
Fatigue is a prevalent symptom in FRDA that may be included in quality of life assessments of individuals with FRDA.	GPP
Physical therapy and exercise training may improve strength, motor performance and reduce fatigue.	GPP
Muscle weakness may interfere with the clinical assessment of coordination and gait in individuals with FRDA.	GPP

2.3 Neuropathy

Author: Dr Marios Hadjivassiliou

2.3.1 Overview

The involvement of the dorsal root ganglion (DRG) in FRDA did not become apparent until the publication of a meticulous autopsy study of a patient with the disease by Mott in 1907 (138). Subsequent neuropathological examinations confirmed reduction in the size of the DRG and demonstrated loss of larger myelinated fibers (113). Sensory neuronopathy is present in up to 98% of patients with FRDA (59). In FRDA the combination of cerebellar ataxia and dorsal root ganglionopathy (also known as sensory neuronopathy) is particularly disabling due to the double impact of cerebellar dysfunction and loss of sensory input resulting in both cerebellar and afferent (sensory) ataxia. In addition to the DRG, there is some evidence of small fiber involvement even in the absence of glucose intolerance (70). As patients with FRDA are more likely to develop diabetes, it is possible that diabetes may also contribute further to the neuropathy but usually at later stages of the disease.

The sensory neuronopathy in FRDA is often severe, correlates with the GAA trinucleotide repeat length (139), is non-progressive (140) however is sufficient to contribute significantly to ongoing disability (sensory ataxia). As the sensory neuronopathy is insidious in onset and long standing, people with FRDA may not necessarily complain of sensory loss but almost always will have features of neuropathy, commonly complaining of cold extremities with clinical evidence of sensory loss on examination.

Whilst the peripheral neuropathy of FRDA is described to be predominantly sensory, there is evidence of motor dysfunction that contributes to weakness. Individuals with FRDA have distal weakness and wasting in the upper and lower extremities (58, 66, 141) Abnormal motor nerve conduction study findings, and/or neurogenic abnormalities on electromyography are rare but occasionally evident in some patients (66, 67, 142). Thus the motor dysfunction in individuals with FRDA is likely to be the result of spinal degeneration (which includes motor neurones). In addition a study by Nachbauer and colleagues reported morphological analysis of muscle biopsies from individuals with FRDA which revealed myopathic, neurogenic and mitochondrial alterations, indicating motor nerves can also be involved in FRDA and may therefore, at least in part, explain the development of muscle weakness in the course of disease (143). (See also section 2.2).

2.3.2 Review of the literature regarding the management of neuropathy in Friedreich ataxia

An extensive literature search did not reveal any specific publications addressing the management of neuropathy in individuals with FRDA. The guidelines proposed are based on a limited number of management guidelines for patients with peripheral neuropathy due to other causes.

Like all other aspects of FRDA, the neuropathy is best managed by a suitably trained health care professional who is familiar with the condition and the management of peripheral neuropathy.

Absence of distal sensation may make the individual more prone to the development of foot trauma leading to ulceration. The most common mechanism of injury is unperceived, excessive and repetitive pressure on plantar bony prominences. Foot deformities, which are very common in FRDA, may contribute to increased focal pressure, making ulceration more likely. Meticulous foot care is important and the input of a podiatrist may be required. This is even more important in those patients with FRDA who also have diabetes mellitus.

Neuropathic pain due to the sensory neuronopathy may be a significant feature in FRDA, however can be treated in the same way as neuropathic pain due to any form of neuropathy. This includes the use of several antiepileptic drugs such as Gabapentin, Pregabalin, Lamotrigine, tricyclic anti-depressant medication such as Amitriptyline and the serotonin re-uptake inhibitor Duloxetine (2, 3).

The reduced mobility and weakness as well as the presence of a sensory neuropathy make FRDA patients more susceptible to focal neuropathies. If such mononeuropathies are clinically suspected then neurophysiological assessment is useful in confirming the mononeuropathy. If bothersome to the patient such entrapment neuropathies can be alleviated by review of activities of daily living and wheelchair positioning, splinting or surgical release.

2.3.3 Recommendations

Recommendations	**Grading**
Neuropathic pain may be treated with Gabapentin, Pregabalin, Lamotrigine, Amitriptyline or Duloxetine.	C (2, 3)
A detailed sensory assessment and examination will establish the extent of neuropathy.	GPP
Protective foot care is important.	GPP
Preventative measures such as review of daily activities, transfers and wheelchair positioning may reduce the incidence of focal neuropathies.	GPP

2.4 Spasticity and Spasm

Authors: Dr Michael Parkinson, Dr S.H Subramony, Dr Paola Giunti.

2.4.1 Overview

Spasticity is the presence of increased muscle tone (hypertonia) caused by a lesion of the upper motor neurons (or pyramidal tracts). Spasticity is distinguished from rigidity because of its velocity-dependent nature and absence of associated extra-pyramidal features. It can cause muscular stiffness, spasms and pain. In conditions which exclusively affect the upper motor neurons (UMNs), it can often be associated with weakness and hyperreflexia. Persistently raised muscle tone can result in abnormal posturing of limbs and other body parts. If this is prolonged, shortening of tendons can occur in the affected body part causing fixed abnormal body positions such as fixed flexion deformities and ultimately contractures.

Spasticity is found in many neurological conditions which affect the UMNs, such as stroke, head injury, spinal cord injury, cerebral palsy, multiple sclerosis and motor neuron disease. Spasticity can affect many parts of the body contributing to many of the problems experienced by individuals with FRDA such as dysarthria, dysphagia, and deficits in the upper and lower limbs such as problems with manual dexterity and gait. In FRDA, because of the coexisting pathological involvement of the dorsal root ganglia and the cerebellum, the exact contribution of spasticity and UMN pathology to the motor dysfunction may be difficult to assess. In addition, involvement of the sensory pathways may mask some of the traditional signs associated with spasticity such as hyperreflexia.

2.4.2 Literature review of spasticity related to Friedreich ataxia

Natural History

There is little epidemiological evidence on the incidence of spasticity in FRDA although personal experience from the clinic suggests that lower limb spasticity and abnormal posturing can be a common and distressing feature of the condition. Indeed, individuals who do not demonstrate spasticity overtly on examination, may well have brisk reflexes once chair-bound and are often bothered by severe flexor spasms, a manifestation of the UMN syndrome. This can severely affect sleep and quality of life. In the late stages of the disease, people with FRDA often develop talipes equinovarus causing difficulties with transfers and wheelchair positioning, and so progressive disability and increased carer need.

Geoffroy and colleagues (63) described 33 patients with ‘typical’ FRDA of whom 15.1% had spasticity. Harding (58) described 115 patients with FRDA from 90 families in the UK. She found 12.2% had increased lower limb muscle tone but none of the patients had increased upper limb tone. Finger contractures were found in 11.3%. Montermini and colleagues (88) studied the phenotypic variability in 100 patients with FRDA including 8 patients with late-onset FRDA (LOFA), 6 patients with FRDA with retained reflexes (FARR) and 44 patients with Acadian FRDA.

Although they did not comment on the incidence of spasticity in the main cohort, the Acadian group included four patients who had spasticity.

Badhwar and colleagues (130) reviewed the literature describing people with FRDA presenting with spasticity. They identified 21 patients, 38% of which had one GAA expansion of fewer than 200 repeats, 33% had a point mutation (either G130V, R165C or R165P) and 10% were homozygous for GAA expansions of greater than 200 repeats. They also described a family in which one individual, homozygous for a 750 GAA repeat expansion, had marked spasticity, but other individuals with similar or smaller expansions had different presentations without spasticity. They concluded that individuals with such 'mid-size' expansions can develop spasticity and that disease course is difficult to predict from expansion size as measured from peripheral blood samples.

It should be noted that most studies, except that by Harding (58), report spasticity affecting lower limbs. Clinically it is apparent that some individuals with FRDA may also present with spasticity affecting upper limbs, warranting further examination.

2.4.3 Literature review related to incidence in Friedreich ataxia.

Late-Onset Friedreich Ataxia (LOFA)

Bhidayasiri and colleagues (144) studied 13 patients with LOFA (defined as having clinical onset of symptoms after the age of 25) and compared them with 13 patients matched for sex and clinical severity. Patients with late-onset disease had significantly smaller GAA repeat size than those with typical FRDA (176±135 vs 490±52 for smaller allele). Lower limb spasticity, retained reflexes, lack of sphincter disturbance and normal echocardiogram were significantly more common in the late-onset group. Klockgether and colleagues, Ragno and colleagues and Gates and colleagues (124, 145, 146) each described a small number of patients with LOFA. In each case, there was an increased incidence of spasticity.

Friedreich Ataxia with Retained Lower Limb Tendon Reflexes (FARR)

Coppola and colleagues (147) studied 101 patients who were diagnosed with a homozygous *FXN* GAA repeat expansion. Of these, 11 (10.9%) had retained tendon reflexes in the lower limbs and were described as having the clinical phenotype of FARR. They varied in age at onset of symptoms from 13 to 45 years. The mean size of the smaller GAA expansion was 408, varying between 120 and 784. Of the 11 individuals with FARR, four (36.4%) had increased lower limb tone.

Acadian FRDA / Acadian Spastic Ataxia

Richter and colleagues (148) studied a milder, more slowly progressive variant of FRDA in 10 Acadian families from New Brunswick, Canada. A recessive ataxia affecting Acadians from the Maritime Provinces of Canada had already been described, which for historical reasons is

linked with a cluster in the Cajun populations of Louisiana, USA (149). Three individuals from two of these families had spastic ataxia.

Compound Heterozygotes with FXN Point Mutations

Gellera and colleagues (150) in their series of 13 compound heterozygotes with one GAA repeat expansion and one of seven point mutations in the *FXN* gene, found mild gait spasticity in one individual with a c.157delC (p.R53AfsX75) mutation. Cossée and colleagues (101) compared the clinical features of 25 such compound heterozygotes from 19 families, with 196 individuals homozygous for the GAA repeat expansion. Those with truncating mutations, or missense mutations in sequences encoding the carboxy-terminal half of the frataxin protein, had a similar phenotype to those with a homozygous GAA expansion. However, individuals with a missense mutation in sequences encoding the amino-terminal half of the frataxin protein (D122Y and G130V) had a milder clinical phenotype with early-onset spastic gait. In addition, these people often had retained upper and lower limb reflexes; no dysarthria and little or no ataxia (refer to section 7 on point mutations/deletions).

It seems therefore that individuals with a relatively short GAA expansion in the *FXN* gene (<200 repeats) commonly have a later age at onset of symptoms and often have an atypical presentation which may mimic progressive spastic paraparesis. Such individuals should be monitored for the development of spasticity, and appropriate interventions put in place. It therefore follows that patients who present with some features of FRDA but who have atypical features such as late onset or retained reflexes, or who present with spastic paraparesis for which no other cause is found, may warrant genetic testing for FRDA which may include testing for compound heterozygous point mutations if heterozygosity for a GAA expansion is found. However, given the considerable phenotypic variability of FRDA, it is highly likely spasticity will still develop in individuals with larger GAA expansions.

2.4.4 Literature review regarding intervention for spasticity

Few trials have been undertaken on interventions for spasticity in individuals with FRDA. Indeed, there is only one case history which described this subject specifically (151). The underlying neurophysiological mechanisms of spasticity and spasms are likely to be similar in FRDA to those in more common conditions, such as stroke and multiple sclerosis, in which spasticity is a more prominent feature and for which there is a greater evidence base. Decisions regarding spasticity management in FRDA therefore need to be made pragmatically on the basis of evidence from other conditions and personal experience. Comprehensive reviews of the management of spasticity in multiple sclerosis (MS) are given in the Clinical Guidelines undertaken by the UK's National Collaborating Centre for Chronic Conditions (2004) and the Cochrane Library (152, 153). Cochrane Reviews also exist for spasticity associated with spinal cord injury (154), amyotrophic lateral sclerosis (154, 155) and cerebral palsy (156, 157).

The purpose of treating spasticity is to maintain mobility, capacity to stand and transfer and upper limb function; to reduce distressing symptoms of pain and spasms, in particular to reduce nocturnal spasms and so improve sleep and prevent fatigue; to facilitate seating,

transferring, toileting or dressing and thereby reduce caregiver burden or reliance, and promote independence; to prevent contractures and thereby reduce the development of long-term disability; and to prevent the development of pressure sores or skin ulceration and so reduce resulting comorbidity.

2.4.4.1 Pharmacological

Medications should be used in combination with patient education and physical therapy. The evidence base for all agents is weak with very few placebo-controlled trials conducted. Oral medications or intrathecal Baclofen may work best for generalized spasticity, whilst intramuscular botulinum toxin or phenol injections can help with more focal problems. In all cases, there can be paradoxical worsening of mobility or functioning, such as in transferring, by reducing spasticity and unmasking weakness (158). We found no evidence of specific trials of oral Baclofen, Tizanidine, benzodiazepines, Dantrolene sodium, Gabapentin, Cannabis extract or Quinine sulphate in FRDA.

Oral Medications

Baclofen

The most commonly used agent is Baclofen. Clinical trials of Baclofen have included patients with stroke, cerebral palsy, spinal cord injury and MS. Although most have shown reduced levels of hypertonia and spasms, few have shown improved levels of functioning. Baclofen should be started at a dose of 5-10mg per day, generally at night due to its sedating side effects. The dose can be increased gradually in three divided doses to a maximum of 100-120mg per day. Side effects include drowsiness, confusion and dizziness. It should be used with caution in the presence of epilepsy as it lowers seizure threshold. Abrupt withdrawal should be avoided as this can cause seizures, anxiety, confusion and hallucinations (159, 160).

Tizanidine

Placebo-controlled trials in stroke, MS and spinal cord injury have shown reduced muscle tone, spasms and clonus, but again have not demonstrated functional benefit. Tizanidine causes drowsiness, dizziness, dry mouth, hypotension, hallucinations but also impairment of liver function tests. It is advised to check these monthly for the first four months and warn patients to seek medical attention promptly if signs of liver failure occur. Abrupt withdrawal should be avoided because of rebound tachycardia and hypertension. It is typically started at 2mg daily and increased gradually in increments of 2mg to a maximum of 36mg in divided doses (159). A meta-analysis suggested that paradoxical weakness is less of a problem with Tizanidine than with Baclofen or benzodiazepines (161).

Benzodiazepines

Several benzodiazepines can be used in the management of spasticity, most commonly Diazepam and Clonazepam. Diazepam has been studied in cross-over and comparison studies

in MS, cerebral palsy and paraplegia with similar efficacy to other drugs. However, the side effects of sedation, respiratory suppression and impairment of attention and memory may limit its use. Tolerance and dependency also frequently occur. Abrupt withdrawal should be avoided as this can precipitate seizures (160). Diazepam can be started at 2mg at night and increased gradually to a maximum of 60mg per day in three divided doses. Clonazepam, which has a shorter half-life than Diazepam, may also be used, starting at 250-500µg at night and increased slowly as tolerated to a maximum of 8mg in three to four divided doses.

Dantrolene Sodium

Dantrolene sodium acts directly on skeletal muscle and can therefore be used in conjunction with centrally acting agents and has the advantage of causing fewer centrally mediated suppressant side effects although drowsiness, dizziness, fatigue and respiratory depression are still possible. The drug can also cause severe diarrhea which should prompt withdrawal. A major limiting side effect is the risk of potentially life-threatening hepatotoxicity, usually at doses of greater than 400mg per day. Liver function tests should be monitored regularly and patients informed how to recognize signs of liver failure and to seek prompt medical attention in this event. It has been studied in stroke, MS, spinal cord injury and cerebral palsy, showing improved measures of spasticity but again no functional benefit (159). Dantrolene sodium can be started at 25mg daily and increased on a weekly basis as tolerated to a maximum of 100mg four times daily. The usual dose is 75mg three times daily.

Gabapentin

There have been a few small trials in MS and spinal cord injury which have shown good tolerability and beneficial effects on measures of spasticity (159). Gabapentin is also used in the treatment of epilepsy, migraine and neuropathic pain, and so if these are also present, Gabapentin may represent a rational treatment choice. Its side effects include gastrointestinal effects, dry mouth, weight gain and dizziness. Abrupt withdrawal may cause anxiety, insomnia and nausea and should therefore be avoided. It is usually commenced at 300mg per day, either at night or in three divided doses, and can be increased gradually to a maximum of 3.6g daily in three divided doses. A common maintenance dose is 300mg three times daily.

Cannabis Extract & Cannabinoids

Anecdotally, it is known that patients sometimes gain benefit from the use of Cannabis products in reducing pain and spasticity in a variety of neurological conditions. This has not been specifically studied in FRDA. The main active ingredient of the cannabis plant, *Cannabis sativa,* is Δ^9-tetrahydrocannabinol (THC). This is available in a synthetic form as an oral preparation (Dronabinol), or as mixed *Cannabis sativa* extract (Nabiximols) as an oromucosal spray. A further synthetic cannabinoid, Nabilone which also has prominent anti-emetic properties, is also available. Previous trials have also been conducted on a further cannabinoid present in *Cannabis sativa*, Cannabidiol (CBD). Side effects have included sedation, dizziness, dry mouth, disorientation and alteration of mood. Cannabinoids should be avoided with coexistent psychotic illness (162).

Extensive studies of *Cannabis sativa* extract and synthetic cannabinoids (including two small trials of Nabilone) have been undertaken largely in MS, but also in stroke, head injury and spinal cord injury. These have largely shown significant reductions in pain, spasms and spasticity. However, by far the largest of these trials (163, 164) which were both randomized, placebo-controlled trials in MS, have failed to show significant reductions in objective markers of spasticity (the Ashworth score) but did show significant reductions in patient-reported measures of spasticity. Further research is required.

Quinine Sulphate

Quinine sulphate is used extensively in the elderly for painful nocturnal cramps which are often associated with spasticity. However, the US Food & Drug Administration recently issued a safety announcement indicating that Quinine sulphate is specifically not approved for the treatment of nocturnal leg cramps because of the risk of serious adverse events including fatalities (165). However, its use continues in other domains, although not commonly in FRDA, perhaps because serious adverse reactions have included cardiac arrhythmias and cardiac conduction defects. Its use is therefore not generally recommended in FRDA.

Other Oral Medications

Many other medications have shown some evidence of efficacy as possible anti-spasticity agents including Methocarbamol, Levitiracetam, Lamotrigine, Pregabalin, Progabide, Clonidine, Piracetam, Vigabatrin, Prazepam, Cyproheptidine, L-threonine, Thymoxamine, Orphenadrine and 3,4-diaminopyridine. There are no specific trials in FRDA.

Intramuscular Botulinum Toxin Injection

Intramuscular botulinum toxin injections are the commonest treatment of focal spasticity although there are no published trials of botulinum toxin injection for spasticity in FRDA.

A recent review of consensus statements on intramuscular botulinum toxin injection in the management of lower limb spasticity considered 23 trials which included 1047 patients with stroke, MS, trauma and other causes of spasticity (4). Numerous well-controlled, randomized trials showed significant improvement in objective assessments of spasticity such as the Ashworth and Modified Ashworth Scales. Most trials have shown efficacy in improving passive function but few studies have demonstrated improvements in active function. The authors concluded that patients should have detailed assessment by a multidisciplinary team who could identify the main presenting impairments such as hypertonia, weakness (in particular weakness that will be unmasked by botulinum toxin), loss of range of joint motion or muscle spasm, and could distinguish muscle overactivity from contracture. They felt that treatment was appropriate if improvements could be realistically expected in areas affecting function and participation such as gait speed, independence in transferring, hygiene and dressing ability; or in reducing impairments such as pain or contractures. They felt that goal-setting in conjunction

with the patient was crucial and that the assessment should identify overactive muscles which could be treated in relation to those treatment goals (4).

Botulinum toxin injection has the advantage of engendering highly focal reductions in muscle overactivity without systemic side effects. Side effects include local injection site reactions, pain, tenderness and bruising. Local diffusion of the toxin can cause unwanted local weakness, such as difficulties in speech and swallowing caused by injection into the sternocleidomastoid muscles for cervical dystonia. Smaller muscles are usually more easily treated than large muscles because of the lower dose required to diminish muscle activity. Thus, toe clawing and forced finger flexion may be easier to treat than hip and knee flexion deformities, although functional improvement such as improved seating posture may still be possible with the latter. The clinical effect of botulinum toxin injections begins gradually over 4-7 days and causes clinically detectable weakness for 3-4 months, with benefit then wearing off gradually. Patients are therefore usually injected at 3-4 month intervals, if symptoms recur. Long term treatment appears to be safe, although efficacy may be reduced by the production of neutralizing antibodies with frequent injections. It is estimated that this occurs in approximately 1 in 200 cases after 1-4 injections (166) but the incidence may be as high as 4% for more prolonged treatment. More than 10% of patients may develop 'botulinum toxin resistance' after prolonged use, with the greatest incidence occurring in patients receiving larger or more frequent doses (167).

There is evidence that the beneficial effects of botulinum toxin injection are augmented and prolonged by adjunctive therapies at the time or immediately after injection, such as stretching, taping, casting, dynamic orthoses or electrical muscle stimulation (4). It is therefore vital that botulin toxin injections are combined with a timely course of physical therapy.

Alcohol and Phenol Injection

Local injection of dilute alcohol or phenol with the intention of chemical destruction of a nerve (neurolysis) has been used in the treatment of focal spasticity but has been largely superseded by botulin toxin injections (159, 168). Neurophysiological guidance is required to identify the target nerve and the procedure can be poorly tolerated especially in children. There is a significant risk of long-term pain, paraesthesiae and even causalgia, particularly if the targeted nerve contains sensory fibers. There may also be local tissue damage causing edema or venous thrombosis. The most commonly used interventions are tibial nerve block for foot deformities, and obturator nerve block for scissoring gait or with the intention of improving perineal hygiene.

Intrathecal Baclofen and Phenol

Ben Smail and colleagues (151) described a 39-year old man with FRDA (heterozygous GAA expansion and T317G point mutation) who had painful and disabling spasms, who was treated successfully with intrathecal Baclofen. The patient had disease onset at age 10 years and lost the ability to walk at the age of 33 years. He had frequent painful extensor spasms and less frequent flexor spasms of the lower limbs and back that periodically ejected him from his

wheelchair. He required two belts to maintain him in the wheelchair and was unable to sleep for more than half-an-hour at a time. Frequent tonic activity of soleus and gastrocnemius was measured by electromyography (EMG) which increased after manual brushing of the soles of the feet. Oral Baclofen (90mg) and Dantrolene sodium (300mg) had been ineffective. A dose-dependent decrease in extensor spasms and associated pain was observed with test injections of 50 to 100µg intrathecal Baclofen. Tonic extensor activity of soleus and gastrocnemius began to decrease 30 minutes after intrathecal injection of 100µg Baclofen, and completely disappeared after 55 minutes. Clinically observed spasms and pain were noted to disappear for 6 hours after intrathecal injection of 75µg Baclofen. The intrathecal Baclofen was very well tolerated. The patient's sleep returned to normal and wheelchair positioning was facilitated. He underwent implantation of an intrathecal Baclofen-delivering pump, providing a continuous dose amounting to 100µg daily. After five months he returned to work, having not been able to work for a year.

There are no systematic trials of intrathecal Baclofen in FRDA. There are however well-conducted, placebo-controlled trials in other causes of spasticity showing benefit particularly in severely disabled individuals with muscle overactivity mainly confined to the lower limbs, such as is commonly seen in FRDA (160). Baclofen is delivered into the intrathecal space via a catheter linked to a programmable pump which is implanted into the abdomen. This has the advantage of requiring far lower concentrations of Baclofen than oral medication and causes fewer systemic side effects. However, the procedure is invasive, expensive and requires long-term continuous monitoring from a multidisciplinary team. The pump reservoir periodically requires recharging and the pump battery replacing. Patients must therefore be selected carefully and usually are those with severe spasticity who have failed other physical and pharmacological methods of spasticity control. Potential response to treatment is usually tested by bolus dose delivery of Baclofen by lumbar puncture or temporary catheter. Complications include local wound or device infection which may necessitate removal of the system. Failure of the pump or catheter can cause a catastrophic and potentially fatal syndrome of abrupt Baclofen withdrawal causing increased spasticity, anxiety, confusion, hallucinations, seizures and hyperthermia (168). The symptoms may be treated with oral Baclofen or other anti-spasmodics whilst the team looking after the pump is alerted.

Intrathecal phenol has also been used but because of the destructive nature of the agent, its use is restricted to those patients with severe lower limb spasticity who cannot be managed by alternative means. Because of the effects on bladder, bowel and sexual function, careful patient selection and informed consent is vital (159).

2.4.4.2 Physical Therapy

We found limited studies specifically investigating the effects of physical therapy on spasticity in FRDA (see section 2.15 on rehabilitation for description of these studies). Several papers describe general rehabilitation strategies in patients affected with ataxia, in most cases resulting from stroke or MS. A fundamental feature of physical therapy management of spasticity is muscle lengthening by passive stretch with the aim of maintaining range and preventing the formation of contractures. This can be achieved temporarily by the physical

therapist, and for more prolonged periods by splinting, casting, orthoses, standing or correct positioning using wedges, cushions and T-rolls. Splinting can involve firm materials or softer supportive substances such as foam, sheepskin or even lycra. However a recent Cochrane Review of stretch as an intervention for the prevention of contractures in those with neurological conditions at risk of developing contractures found moderate to high quality evidence to indicate that stretch does not have clinically important immediate, short-term or long-term effects on joint mobility (5). There was also little or no effect of stretch on pain, spasticity, activity limitation, participation, restriction or quality of life. Thirty-five studies with 1391 participants met the inclusion criteria, but no study performed stretch for more than seven months. The authors could therefore not comment on the effects of stretch performed for more than this time.

Good quality, well-fitted orthoses prepared in a specialist Orthotics Department is also important, if indicated, in the management of spasticity (see also section 2.4). Promoting the strength of muscles by active exercise which antagonize the overactive spastic muscle is also important in reducing spasticity. Again, correct positioning may optimize the functioning of muscle groups which can work to counteract spasticity. Weights and resistant devices can be used to promote muscle strength. Active exercise is generally more effective than passive exercise, if the patient is able, and the consequent increased cardiovascular fitness helps to combat fatigue and allows further exercise. Repeated practicing is used to reinforce motor learning which improves function. If one limb is more profoundly affected than the other, it may be beneficial to constrain the better limb, forcing the weaker limb to undertake more work, and thus strengthen it. Conversely, compensatory techniques may be taught to allow the patient to function optimally. There is some evidence for electrical stimulatory devices in the treatment of spasticity, including the Functional Electrical Stimulator, the Foot Drop Stimulator and the Transcutaneous Nerve Stimulator (159, 169).

Physical therapists have a critical role to play in educating patients and caregivers as to correct posture, muscle use and the identification and avoidance of features which aggravate spasticity such as tight clothing, poorly adjusted wheelchairs, pain and infection. Physical therapy has to become ‘a way of life’ for the patient. Therapists should also promote motivation, positive thinking and psychological support (see Figure 1).

2.4.4.3 Surgical Treatment

Surgical treatments are generally considered options of last resort when physical and pharmacological interventions have failed, however, in exceptional cases, particularly in the case of a fixed, non-reducible deformity, they may be considered.

Orthopedic Procedures

If severe hypertonia results in established limb deformities such as ankle equinovarus, orthopedic procedures such as tendon lengthening, tenotomy or tendon transfer may be indicated. Delatycki and colleagues (6) studied 32 patients with FRDA and equinovarus deformity of the foot. They were assigned to three groups: mild, requiring splinting alone (15);

moderate but reducible, requiring botulinum toxin injection (8); and severe and not fully reducible, requiring surgery (9). Seven patients ultimately went on to have surgery involving lengthening of the Achilles tendon to correct the equinus deformity, and transfer of the tibialis posterior tendon to peroneus brevis to correct the varus deformity. None of these was able to stand to transfer independently before surgery, whereas all seven were able to do this post-operatively. None was able to walk independently after surgery. Transfers and mobility subscales of the Modified Barthel Index and the Functional Independence Measure showed significant change between the pre- and post-operative periods. Three patients had significant surgical complications (two cases of aspiration and one of pulmonary embolus requiring plasminogen activator) but each recovered fully. The authors recommended aggressive management of foot deformities.

Neurosurgical Procedures

With the exception of intrathecal Baclofen pump insertion, the neurosurgical treatment of spasticity is only considered if all other medical and physical methods have failed. Procedures include peripheral neurotomies, dorsal rhizotomies and microsurgical ablation of the dorsal root entry zone ('DREZotomy'). It is mainly indicated when patients have focal spasticity without useful mobility, and ablation of specific nerve fibers will result in improvement in a specific focal symptom, such as tibial nerve ablation for equinovarus deformity of the foot. It is therefore vital to have clear functional goals, such as decreased pain, improved comfort or improved posture or transferring. All these methods are now very rare as the techniques are destructive and irreversible, and the results variable. Inserted neurostimulators of the cervical spinal cord and cerebellar cortex were also previously used, largely in cerebral palsy. No trials have been conducted in FRDA (170).

2.4.5 Recommendations

Recommendations	Grading
People with FRDA may benefit from assessment for spasticity, pain and spasms (including nocturnal spasms) and incipient or established contracture. This may guide treatment.	GPP
On implementation of an anti-spasticity intervention, individuals with FRDA may benefit from reassessment as the treatment of spasticity can unmask weakness and cause deterioration in gait and standing transfers. Individuals should be warned of this phenomenon before anti-spasticity interventions are commenced.	GPP
Aggravating factors such as infection, pain, constipation, diarrhea, dehydration and pressure sores should be considered and treated in the context of acute onset or exacerbation of spasticity and/or ataxia.	GPP
Spasticity and spasms should be treated at an early stage, initially by non-pharmacological means. If these are unsuccessful, pharmacological means such as the use of Baclofen, Tizanidine,	C (4-6)

Benzodiazepines, Dantrolene sodium, Gabapentin, botulinum toxin injections, alcohol and phenol injections or intrathecal Baclofen pumps may be considered. The benefit of such compounds must be balanced against adverse effects they might produce on other symptoms of FRDA (for example ataxia). In the last resort, surgical options may be considered. The distribution of spasticity around the body may also determine which intervention is chosen.	
Individuals with FRDA, families and caregivers should be educated to monitor the development of spasticity and incipient contractures, and should be given an ongoing plan of exercises and passive or active stretching to be performed routinely outside the clinical setting.	C (4)

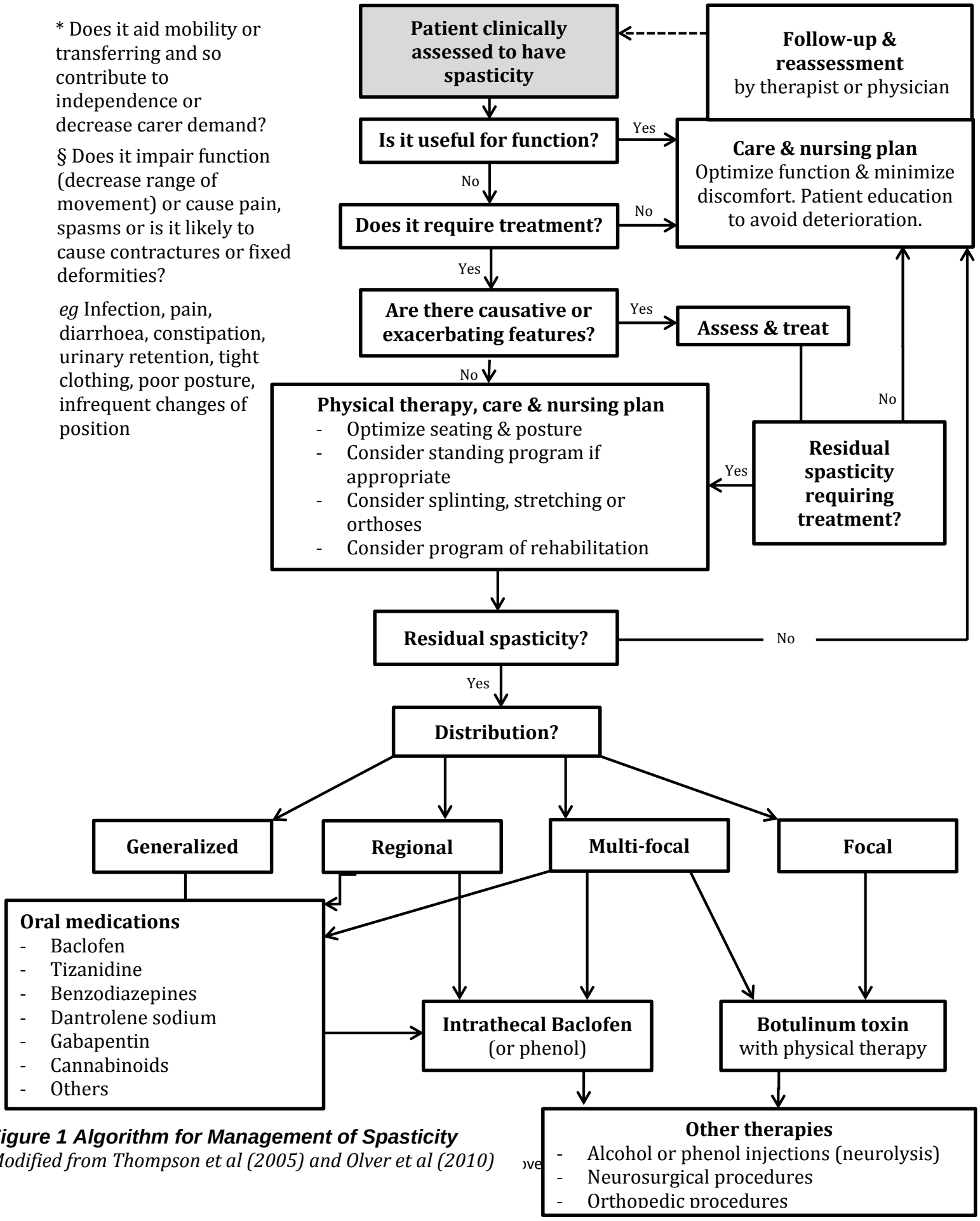

Figure 1 Algorithm for Management of Spasticity
Modified from Thompson et al (2005) and Olver et al (2010)

2.5 Restless Legs

Author: Dr Mary Kearney

2.5.1 Overview

Restless legs syndrome (RLS) is sometimes called Ekbom's syndrome after the doctor who first described it in 1945. It is a common neurological motor disorder whose complex pathophysiological background is not yet fully understood. Adult studies report a prevalence varying from 2% to 15%. It is more common in women and older adults. It is characterized by an irresistible urge to move the legs that is associated with unpleasant sensations in the legs.

The International Restless Legs Syndrome Study Group (171) developed standardized criteria for the diagnosis of restless leg syndrome in 1995 and these criteria were further modified in 2003. They are:

- An urge to move the legs
- That is present at rest
- Relieved by movement and
- Demonstrates a circadian pattern with peak symptoms occurring at night or in the evening.

In 2009, Hening and colleagues identified a variety of conditions, including leg cramps, peripheral neuropathy (which is present in FRDA), radiculopathy, arthritic pain, positional discomfort and pronounced or frequent unconscious foot or leg movements which can satisfy all four diagnostic criteria for RLS and thereby mimic RLS (9). Hening and colleagues suggested the following criteria is required to confirm RLS (9). Symptoms are:

- Persistent, not fleeting
- Not readily relieved by a simple postural change
- Not precipitated by their legs being in a specific position
- More distressing if the legs are restrained and confined when symptoms are present
- Associated with sleep dysfunction.

The underlying cause of RLS is not understood, but thought to be associated with the dopaminergic system and depletion in iron stores. In most people, RLS is idiopathic but 50% have a family history suggesting a genetic basis. Secondary causes of RLS include pregnancy, iron deficiency, renal failure and a wild range of other conditions e.g. Parkinson disease, peripheral neuropathy, hypothyroidism, diabetes. Drugs can exacerbate RLS, most particularly antidepressants, neuroleptics, dopamine blocking anti-emetics e.g. Metoclopramide, sedating anti histamines and calcium channel blockers. Given the presence of peripheral neuropathy and multisystem neural dysfunction in FRDA it is unsurprising that some people with FRDA experience RLS.

2.5.2. Description of the natural history

Two recent cross-sectional studies have shown a greater incidence of RLS in people with FRDA (32% to 50%) compared to the general population (2% to 15%) (7, 8). Both these studies evaluated people with typical FRDA. There is currently no published longitudinal study on the natural history of RLS in FRDA.

Synofzik and colleagues (7) studied 28 people with FRDA and 28 age matched control. All participants underwent a structured interview, standardized examination to exclude "mimics", detailed drug history and laboratory blood tests including serum ferritin. In addition transcranial sonography was performed to assess the echogenicity of the substantia nigra by independent and experienced examiners who were blinded to the RLS assessment. Nine of the 28 (32%) participants fulfilled the criteria for RLS, but only one of them had ever been treated with dopaminergic drugs.

Frauscher and colleagues (8) studied 16 consecutive patients with FRDA for RLS. All participants underwent the standardized neurological examination SARA and FARS, routine laboratory tests and a structured sleep history. RLS mimics were excluded. Eight hour polysomnography was performed during two consecutive nights. Eight of the 16 (50%) participants had RLS, and these eight had a significantly lower serum ferritin than those with FRDA who didn't have RLS. Results from the sleep studies were inconclusive.

2.5.3 Current investigation for restless legs in Friedreich ataxia

Diagnosis of RLS is based on fulfilling the four criteria and the supplementary questions outlined in section 2.5.1. Laboratory investigations should be guided by history and examination and would usually include:

- Full blood count, renal function, thyroid function, glucose and vitamin B12
- Serum ferritin level

2.5.4 Intervention for restless legs syndrome

If there is a secondary treatable cause, this should be treated. If serum ferritin is < 50 mcg/ml treat with iron. Renal failure or inflammatory disease may cause raised ferritin since it is an acute phase reactant. Therefore transferrin saturation should be assessed and if < 20%, it suggests iron deficiency which is a common secondary cause of RLS that is easily treated with iron supplementation.

No study has been published on the treatment of RLS and FRDA. Several studies have examined the efficacy of dopaminergic substances in RLS in populations without FRDA. However, only a few studies have examined treatment effects longer than 12 weeks. Levodopa trials were conducted mainly in the 1990s using a cross-over design with few included patients. Clinical experience revealed the most serious side effect of dopaminergic treatment is the development of augmentation. This was first described by Allen and colleagues (172).

Augmentation is characterized by an overall increase in severity of RLS symptoms that can be seen in an earlier onset of symptoms during the day, faster onset of symptoms when at rest, spreading of symptoms to the upper limbs and trunk, and shorter duration of the treatment effect (10). However, no study has examined long-term effects (i.e. longer than one year) of prescribing dopaminergic medication. Two Cochrane reviews have been published in 2011 on this subject. The Cochrane reviews did not differentiate between treating idiopathic and secondary RLS and highlighted this issue.

2.5.5 Recommendations

Recommendations	**Grading**
People with FRDA should be specifically asked if they have RLS symptoms	B (7, 8)
A full history of the symptoms should be taken from patients suspected of having RLS so that other confounding conditions i.e. periodic leg movements can be excluded.	B (9)
Secondary causes of RLS should be excluded, in particular, a drug history should be taken and serum ferritin should be undertaken.	B (9)
Initial treatment of RLS should consider the needs of the patient, the severity of the symptoms, the relative significance of the reported effects of the treatment and the level of dysfunction attributable to RLS.	A (10)

2.6 Mobility

Authors: Ms Sarah Milne, Ms Emma Campagna, Dr Louise Corben

2.6.1 Overview

In clinical practice, mobility is defined as the ability to move from one point to another and can be classed as gait, ambulation, transferring, wheelchair mobility and bed mobility. Mobility may be independent or assisted. Spinal cord, peripheral nerve and dorsal column degeneration may occur early in FRDA causing afferent ataxia considered the primary cause of early decline in mobility (12, 173). In addition, dorsal column degeneration causes impairment in proprioception and vibration sense, both of which play a critical role in establishing the timing and magnitude of muscle activity during locomotion (174-177). The spinocerebellum is responsible for integrating sensory input with voluntary motor action. This ensures coordinated and automated timing, duration and amplitude of muscle activity in normal movement, enabling stable and accurate limb movement (178). The cerebellum also has a role in the dynamic regulation of balance and adaptation of posture and locomotion through practice and is critical in locomotion (179-181). Hence cerebellar pathology also contributes to a decline in mobility in people with FRDA (173).

Muscle weakness may also contribute to impairment in mobility (12, 182). However, decline in muscle strength may not directly correspond to loss of ambulation as evidenced in a study by Beauchamp and colleagues (1995) who reported mean lower limb strength was 70% of normal at the time people with FRDA began to use a wheelchair (183). Weakness tends to affect the pelvic girdle first and then progresses to the lower limbs and trunk (183). A further contributing factor in the decline in mobility in people with FRDA is spasticity of calf and foot musculature (177, 184, 185). Spasticity causes co-activation of agonist-antagonist muscles, loss of selective motor control, and impaired sequencing and timing between muscles, all of which impact on balance control and locomotion (133, 185). Moreover, as a consequence of spasticity, agonists are held in a shortened position whilst antagonists are held in a lengthened position potentially leading to structural changes within the muscles (186). In individuals with FRDA this may result in equinovarus deformity, toe clawing and pes cavus (184). Changes in foot posture may also occur secondary to the inability to transfer weight across the full surface of the foot and the associated influence of plantarflexion hypertonia on the calf musculature and plantar fascia (187).

Equinovarus deformities place individuals with FRDA at a particular mechanical disadvantage and make locomotion, transfers and standing difficult (6, 184, 188). In ambulant individuals, equinovarus deformity renders placement of a flat foot on the ground problematic which exacerbates the balance impairment already present. This may result in use of mobility aids at an early stage of disease progression. In non-ambulatory individuals the equinovarus deformity interferes with a stable base on which individuals stand to transfer leading to an increased dependency on equipment and others to ensure safety during transfers (6).

Spasticity and poor foot alignment can also affect other joints in the body, causing changes to joint mechanics and muscle imbalance. A common occurrence for people with FRDA is knee hyperextension during standing caused by a reduction in anterior translation of the tibia due to gastrocnemius and soleus spasticity and/or contracture (187). Lack of anterior translation has a significant impact on the capacity to transfer from a sitting to standing position (187).

Over the course of the disease, the capacity to independently mobilize diminishes until the individual with FRDA becomes wheelchair dependent (189). As a result of this reduction in mobility, other issues related to de-conditioning occur and can also impact on the ability to mobilize, be it walking, transferring or using the trunk to stabilize in the wheelchair. Please refer to section 2.15 for details on deconditioning.

Key transitional events for people with FRDA regarding mobility are recognition of symptoms, fear of falling and changes to mobility status (189). These transition events usually related to disease severity, can be divided into three subgroups: people who are ambulant, people transitioning from walking to wheelchair and, people who are wheelchair dependent (190).

For most people with FRDA the fear of falling arises from a previous fall or near falls (189). Fear of falling can limit participation in activities and can cause anxiety about social stigmatization (189). Changes involving mobility status may represent the final transition within the FRDA experience (189). Individuals with FRDA may use furniture, walls or the assistance of a person and eventually require a gait aid to assist with locomotion and transfers (177). Initially a gait aid may be used for all mobility however as gait deteriorates, use of a gait aid may be confined to the home with use of a wheelchair for community activities. Conversely some individuals with FRDA decide to move straight to wheelchair use if ambulation with a gait aid is not acceptable. This transition may be associated with increased freedom and independence as mobility is safer and not as physically or mentally exhausting (189). Moreover, earlier disease onset correlates significantly with faster progression to the use of a gait aid and wheelchair and transition to wheelchair is more likely to occur earlier in females (191). The length of GAA expansion in the smaller allele was found to negatively correlate with age at which difficulty with walking becomes apparent, the age at which difficulty walking interferes with activities of daily living and the age at which individuals begin using an assistive ambulation device (191). Klockgether and colleagues suggest faster progression to wheelchair may in part be related to an inability to cope with the physical disability and not just the biological cause alone (191).

For those wheelchair dependent individuals with FRDA, ongoing independence is compounded by decline in the capacity to stand and transfer. This may result in the requirement of use of assistive aids (such as a hoist) or significant help from other people for transferring. Simultaneously, with the gradual decline in ability to transfer, individuals with FRDA may lose their ability to sit independently, firstly relying on their upper limbs to provide balance, then as the disease progresses, may be unable to use upper limbs to maintain balance thus requiring an extra supportive wheelchair.

2.6.2 The pattern of gait disturbance in Friedreich ataxia

The inherent nature of the gait ataxia in FRDA is evidenced by impairment of amplitude of central displacement, directional accuracy and control of the force of movement (192).

To date there are four published studies which have examined the gait pattern in people with FRDA. Croakin and colleagues reported an increase in double stance time, where the transfer of weight from leg to leg is very slow in people with FRDA, as compared to those without disability (193). Increase in double stance time is a well-established motor strategy aimed at compensating for the wide oscillation of the center of mass and is indicative of poor dynamic balance and stability (194). An increase in double stance time appears to occur quite early in the disease and progressively increases as the person with FRDA gets older (193). Reduced time in the swing phase of gait and greater time on the stance leg may also reflect compensation for reduced ability to maintain balance whilst elevating and progressing the leg forward during walking and avoids the most unstable body configuration of single leg stance (193, 194). In examining ambulatory gait kinematic and kinetic values in adolescents and adults with FRDA, Serrao and colleagues, observed gait parameters to be quite variable (194). The main features of the gait pattern were increased double support duration, wide-based walking, decreased speed of walking, increased stance duration, reduced swing velocity and reduced step length. Croakin and colleagues also observed longer gait cycles, significant increase in stride, stance phase and double support sub-phase durations, slower swing velocity and gait speed, shorter step length and greater step width in ambulant children and adolescents with FRDA (193). People requiring assistance with mobility or requiring a gait aid had an even greater increase in double stance phase and a reduction in stride length and velocity (193). The increase in stance phase may be due to the use of a gait aid, which is normally moved whilst the individual is in double stance phase (193). A decrease in gait speed and slower cadence as the individual gets older is likely to also correspond to an increased need for assistance while mobilizing (193).

Serrao and colleagues reported minimal differences in the mean values of the discrete kinematic and kinetic parameters of gait and these differences were mainly around the ankle and hip joints with peak ankle plantarflexion and positive values of hip extensor impulse for people with FRDA compared to unaffected controls (194). The main difference in gait pattern appears to be the increased variability of all global and segmental parameters, indicating reduced temporal inter-joint coordination. A highly irregular alternating proximal/distal joint leading pattern was a significant feature of gait pattern for people with FRDA (194).

Gouelle and colleagues developed the Gait Variability Index (GVI), a ratio to quantify the variability of spatiotemporal parameters during gait, and subsequently investigated its concurrent validity on a sample of 31 people with FRDA using a GaitRITE mat. Spatio-temporal parameters including step length, stride length, step time, stride time, swing time, stance time, single support time, double support time and velocity were used to calculate the GVI (195). Compared to a sample of 123 control subjects, the GVI was 30 points lower in individuals with FRDA indicating a separation of three standard deviations from the healthy population score of

gait variability. The GVI correlated significantly with ICARS total score, ICARS gait and posture subscore, the 25FWT and the Functional Ambulation Performance score, but not with muscle strength. The moderate correlation between GVI and timed gait scores suggests these outcome measures evaluate similar constructs however perhaps assess different elements of neurological function that contribute to effective gait.

Finally, Milne and colleagues recently reported the relationship between spatiotemporal gait parameters and clinical markers of disease severity in 13 people with FRDA (196). Significant correlations were found between the score on the Friedreich Ataxia Rating Scale (FARS), GAA1, age at disease onset, disease duration and spatiotemporal gait parameters such as gait speed and cadence. Interestingly the spatiotemporal gait parameters of increased speed, cadence and step length were positively correlated with an earlier age of disease onset. Moreover, a later age of disease onset was related to a greater time spent in double support, a strategy reportedly used to maintain balance. Milne and colleagues suggested this may be indicative of those people with increased disease severity having a reduced ability to compensate for a deteriorating gait pattern early in the disease process, as compared to those with later onset who are able to enjoy a more stable gait pattern for a longer period.

2.6.3 Intervention for mobility in Friedreich ataxia

Table 4 provides a brief overview of each article related to this topic.

There is limited evidence regarding intervention to improve mobility in people with FRDA. A recent study by Milne and colleagues (2012) found that inpatient rehabilitation improved the capacity to transfer and ambulate (14). Ilg and colleagues showed significant improvements in ataxia symptoms compared to baseline scores in individuals with degenerative cerebellar and afferent ataxia, both immediately and eight weeks after intensive coordinative training (133). For the individuals with afferent ataxia, which included three people with FRDA, there were improvements in balance measures, however no significant improvement in gait. In a study by Delatycki and colleagues, surgery to lengthen the Achilles tendon and tendon transfer to correct equinus deformity improved mobility and standing transfers (6). In two single case studies, a 12 month period of physical therapy did not improve gait parameters however use of a walking aid appeared beneficial in reducing falls and orthopedic shoes combined with physical therapy for one month improved walking distance, reduced falls, improved stability and increased gait speed, step length and cadence (197, 198) (See Table 2).

2.6.4.1 Rehabilitation

Rehabilitation can be beneficial in improving mobility for people with FRDA (14, 199). Rehabilitation consisting of balance and gait retraining and foot sensory stimulation can improve both subjective and clinical outcome measures of static and dynamic balance parameters immediately post-training for people with a clinically defined sensory ataxia secondary to either chronic neuropathy or multiple sclerosis (200). Please refer to section 2.15 of these guidelines for further detail.

2.6.4.2 Physical Therapy

Physical therapy has an important role in assessing and treating symptoms that affect gait. Physical therapists are involved in the prescription of gait aids, recommendations for orthotics, development of home exercise programs and provide therapy and education. Physical therapists address both the neurological symptoms of FRDA as well as the secondary musculoskeletal deficits through strengthening and stretching programs, balance retraining in sitting and standing, aquatic therapy, spasticity management, gait re-education and strategies to prevent falling (11, 12) (see also 2.4.4.2)

2.6.4.3 Multidisciplinary Clinic Management

A multidisciplinary clinic for individuals with FRDA providing regular annual review and management that involves review of mobility including gait aid utilization, orthotic prescription, spasticity management and rehabilitation/exercise requirements can delay early progression to wheelchair (177).

2.6.4.4 Gait aids

As the disease progresses and gait worsens, gait aids become necessary for facilitating safe, upright locomotor function, maintaining mobility and to prevent the deleterious effects of immobility by increasing the base of support and thus stability during mobility (201, 202). Gait aids are used to enable the person to mobilize as independently as possible without assistance. Gait aids may include (in supportive order): single point stick, four wheeled frame, bariatric frame (see also 9.3).

2.6.4.5 Impact of Core stability on mobility

Core stability is essential for proper load balance within the spine, pelvis, and kinetic chain. The so-called “core” is the group of trunk muscles that surround the spine and abdominal viscera. Abdominal, gluteal, hip girdle, paraspinal, and other muscles work in concert to provide spinal stability. Core stability and associated motor control have been shown to be imperative for initiation of functional limb movements, therefore any weakness of these muscles can impact on a person’s ability to mobilize effectively and independently (203). Reduced core stability may contribute to spinal instability which in turn also impacts on the ability to maintain dynamic balance and thus mobility (204). People with FRDA tend to have weakness in the core stability muscles which then causes problems with balance that can affect their ability to mobilize (183). To date there are no known studies examining the impact of reduced core stability in people with FRDA, moreover there are no studies examining the effects of core stability training for this group of people. There is, however limited research demonstrating the benefit of core and trunk stability training on mobility in people with like neurological conditions such as stroke, cerebellar ataxia and acquired brain injury (205-207).

2.6.5 Stages of mobility and evidence for intervention

2.6.5.1 Locomotion

Given the lack of direct evidence in intervention for impairment in ambulation in people with FRDA it is appropriate to review literature on the usual treatment of the components of gait and mobility impairment in other neurological conditions. Rehabilitation for locomotion and mobility can take a compensatory or restorative approach (181). Carr and colleagues (13) described a number of well-established motor strategies aimed at compensating for the wide oscillation of the center of mass and associated difficulties with balance. Missaoui and colleagues (200) have also demonstrated that sensory input and dynamic and static balance retraining can improve balance and mobility measures in people with afferent ataxia. The treadmill with body weight support and parallel bars may also be useful modalities in improving and maintaining locomotion (207-209). Adequate sitting balance and trunk control and coordination is vital for all movement, including walking, standing, transferring and upper limb function. From early on in the disease process emphasis on rehabilitation and maintenance programs for trunk posture, alignment and control in an individual with FRDA is critical.

Orthotic Prescription

Ankle foot orthotics (AFOs) may be appropriate for people with FRDA in order to provide mediolateral stability at the ankle in stance phase, facilitate toe clearance in swing phase, promote heel strike at initial contact, prevent foot deformity, support normal joint alignment and biomechanics, improve range of motion and to facilitate function (210, 211). There are no studies specifically looking at orthotic prescription for people with FRDA, however there are multiple studies describing the benefits of AFO prescription in improving postural security and movement, increasing weight-bearing percentage, improving knee control, reducing toe clawing, improving gait parameters and improving standing and balance in individuals with other neurological conditions such as stroke and spastic cerebral palsy (185, 210-215).

Botulinum toxin injections

The presence of lower limb spasticity often causes secondary complications, such as ankle and foot deformity, which reduce mobility and independence (216). In clinical practice, botulinum toxin can reduce spasticity resulting in reduced foot deformity to enable appropriate weight-bearing (12, 110) (see section 2.4.4.2).

2.6.5.2 Transitioning to Wheelchair

Earlier progression to full-time wheelchair use in a person with FRDA may introduce secondary issues related to reduced mobility, non-use and deconditioning. Hence facilitating ambulant mobility for as long as possible is advantageous to the overall health and well-being of the individual with FRDA (178). During and after transition to full time wheelchair use, it is essential that individuals with FRDA maintain the capacity to transfer safely and independently for as long as possible, particularly as length of time since disease onset and time since full time wheelchair use have been shown to be major indicators for severe deformity requiring intervention (6). Despite transitioning to full time wheelchair use, a program incorporating gait

practice with aids or assistance or use of standing frames or tilt tables can be of benefit in preventing further decline and help maintain ankle range and movement (12, 217).

To minimize decline in mobility due to spasticity of calf and foot it is critical that appropriate physical therapy assessment and treatment of the foot and ankle occurs throughout the individual's lifespan (184). As the person with FRDA becomes more dependent on a wheelchair, calf spasticity and equinovarus deformity may become more evident. Early treatment may prevent secondary complications and minimize the need for more drastic intervention (6). Assessment may include visual observation during mobility in addition to well-known outcome measures for spasticity such as the Ashworth scale (218). Intervention may consist of orthotics, serial casting, pharmacological management, strengthening, functional gait and standing balance re-training and surgery (See 2.4.4).

2.6.5.3 Full time use of wheelchair

This stage of the disease sees the person with FRDA relying on a wheelchair for all forms of mobility. It is critical the capacity to step transfer is maintained as this capacity enables the person with FRDA greater freedom of movement, for example moving in and out of a car. Difficulties in transferring can be attributed to impaired standing balance reduced sensation and an inability to time and grade muscle force appropriately (13). At this stage, emphasis of intervention is on preventing falls, practicing appropriate weight-shifting and standing balance exercises and gait aid prescription. If a person can no longer hold themselves in standing, the focus is on ensuring a 'pivot' transfer is safe and effective. Ensuring the shoulder is not placed in a position of impingement during transfers, maintaining foot contact with the floor and encouraging a forward lean all assist in increasing the efficiency of the transfer and prevents shoulder pain (219-221). Wheelchair prescription is also very important in maintaining mobility in people with FRDA. The correct wheelchair will aid sitting posture, balance and mobility (181). (See 9.3).

As symptoms progress, considerations regarding reduced coordination and strength of the upper limb and trunk, reduced trunk control and lack of sitting balance need to be considered (183). Lower limb strength, management of spasticity and addressing incoordination are also important after the individual with FRDA has ceased ambulating. As the disease progresses, particular and specific movement patterns while transferring may be adopted by the person with FRDA. People with FRDA may have established movement patterns and may have difficulty adapting to a new movement pattern. This may be due to motor learning difficulties (177, 179, 181, 222). Despite the need to minimize clinical risk it is important to assess the movement pattern unique to the individual with as little 'hands on' assistance as possible. Even minimal contact may change the movement pattern normally undertaken by the individual. It should be noted that intervention aimed at changing the movement pattern to a more 'normal' pattern may not be as effective as strengthening the ability in the movement pattern preferred by the person with FRDA.

In clinical practice the use of a slideboard to improve transfers with individuals with FRDA has not been successful. This is likely due to increased motor demands in the setting of significant

truncal ataxia during slideboard placement, in addition to the potential instability of the actual slideboard during the process of transferring.

People with progressive neurological disorders are at risk of respiratory infections and aspiration as their ability to swallow, cough and clear secretions effectively may be limited (223). In order to reduce risk of respiratory infections therapy, aimed at improving sitting balance and trunk/neck/upper limb control is most beneficial for maintaining respiratory muscle strength and position (223, 224).

Serial Casting

Serial casting is used to improve foot posture when weight-bearing by the lower limbs is not effective in improving ankle/foot range of movement for people with FRDA. Its major benefit is the prolonged stretch, more than six hours per day (225). To date, there is no published evidence related to serial casting for people with FRDA, however in the stroke population it has been shown to improve spasticity and endurance after botulinum toxin injections (225, 226).

Standing frame/tilt table

The physiological benefits of a standing program and early weight-bearing have been well documented across a variety of disorders. They include prevention or improvement of lower-extremity contractures, reduction of spasticity to improve functional transfers and mobility, maintenance of bone density, as well as improved circulation, improved respiratory function, reduced incidence of urinary tract infections and increased gastrointestinal motility. A standing frame may be of benefit to people with FRDA, however to date the efficacy of the use of standing frames in the treatment of people with FRDA has not been evaluated (12). Two studies evaluating prolonged standing in children with cerebral palsy and people with spinal cord injury found that increased tone was inhibited and spasms were reduced, with effects lasting between 35 minutes and more than 12 hours (217, 227).

2.6.6 Future direction for research

This guideline has highlighted the paucity of evidence investigating the effects of intervention on mobility in people with FRDA. Further evaluation of the deterioration of mobility and locomotion is vital to aid clinicians with clinical decision making throughout the disease process. There is a need to evaluate interventions throughout the individual's lifespan and at different stages of mobility to determine most appropriate intervention to maximize and maintain independent mobility for individuals with FRDA.

2.6.7 Recommendations

Recommendations	Grade
Mobility, balance, core stability, trunk control, spasticity, foot position and strength should be assessed by a suitably qualified physical therapist.	GPP
The impact of spasticity of lower limbs on mobility should be evaluated when assessing gait.	GPP

Foot and ankle posture should be assessed by a suitably qualified physical therapist and treated proactively.	D (11, 12)
Strategies such as an appropriate exercise program, aquatic physical therapy and stretches may be implemented to prolong ambulation and reduce the number of falls in people with FRDA.	D (13, 14)
Individuals with FRDA dependent on a wheelchair for mobility may still benefit from rehabilitation to improve their mobility.	D (14)
Botulinum toxin and prescription of ankle-foot orthotics may be useful in reducing the impact of spasticity during mobility and will help maintain good foot alignment for mobility.	GPP
Gait aid provision may prolong the capacity to walk. A heavy/weighted gait-aid may be a beneficial for some individuals with FRDA.	GPP
Standing frame and tilt table may be used to maintain foot alignment to enable independent transfers.	GPP
An inpatient rehabilitation program may prolong mobility and transfer ability.	D (14)

Table 4 Summary of studies evaluating intervention on mobility in people with Friedreich ataxia.

Authors	Article Title	Study Type	Participants	Intervention	Outcome Measures	Conclusion
Harris-Love et al (197)	Rehabilitation management of Friedreich ataxia: lower force extremity force-control variability and gait performance.	Case Study	N=1. 14 y.o. with FRDA, mobility with rolling walker and wheelchair.	12 month period of two sessions per week of physical therapy for task orientated reaching activities, muscle stretching, functional strengthening, therapeutic exercise for hip and trunk musculature and gait training with U-Step Walking Stabilizer (USWS).	Nine-hole peg test, single leg stance time, manual muscle testing, gait parameters.	Progressive decline in gait parameters. USWS appeared beneficial in reducing falls.
Delatycki et al (6)	Surgery for equinovarus deformity in Friedreich's ataxia improves mobility and independence.	Prospective cohort	N=36 individuals with FRDA (n=9 for surgery). Exclusion criteria: end stages of the disease.	Lengthening of Achilles tendon and tendon transfer surgery to correct equinus deformity.	Subscales from MBI, FIM	Surgical intervention can improve mobility and standing transfers.
Goulipian et al (198)	Orthopaedic shoes improve gait in Friedreich ataxia: a clinical and quantified study.	Case Study	N=1. 26 y.o female with FRDA. Able to ambulate with a stick. Pes cavus and clawed toes.	Orthopedic shoes for one month.	Clinical gait assessment, quantified gait assessment, self-assessment	Improvement in quality of life as reported by the participant. Increased speed of gait, step length and cadence.
Ilg et al (133),	Intensive co-ordination training improves motor performance in degenerative cerebellar disease.	Intra-individual control design, prospective cohort study	N=16 (FRDA n= 3). Degenerative cerebellar disease. Inclusion criteria: able to ambulate with aid or no aid	One hour session, three times per week for four weeks. Static balance, dynamic balance, whole body movement and treatment of	SARA, ICARS, GAS, VICON, BERG balance test, gait measures	Improvement in multi-joint co-ordination and dynamic balance with intensive training. Maintenance of improvement if a home exercise program is performed by the participant.

				contracture if applicable.		
Milne et al(14)	Retrospective study of the effects of inpatient rehabilitation on improving and maintaining functional independence in people with Friedreich ataxia	Retrospective Cohort Study	N=29. All people admitted to inpatient rehabilitation with FRDA at rehabilitation hospital from 2003-2010.	Multidisciplinary inpatient rehabilitation for a variable time, length based on the patient's goals.	FIM	Function improved after rehabilitation and was maintained or continued to improve for the immediate time period following rehabilitation intervention.

Legend
SARA – Scale of the assessment and rating of ataxia
ICARS – International cooperative ataxia rating scale
VICON- Vicon motion measurement system
BERG – Berg balance test
MBI- Modified Barthel Index
FIM – Functional Independence Measure
USWS - U-Step Walking Stabilizer

2.7 Dysarthria

Authors: Dr Adam Vogel, Ms Melissa Loucas, Ms Lucy Rodriguez, Dr Paola Giunti

2.7.1 Overview

Speech difficulties (dysarthria) are a primary feature of FRDA. People with FRDA often present with a reduced rate of speech, vocal instability, mixed nasal resonance and imprecise consonants (15). These difficulties can affect an individual's ability to communicate with others.

There is some evidence suggesting the existence of three subgroups of speech profiles among individuals with FRDA (15, 228). Approximately a third of individuals are characterized by mild articulatory imprecision leading to a mild reduction in sentence intelligibility and communicative efficiency. The remaining two subgroups reflect more severe dysarthric impairments, with each group significantly differing from the primary subgroup with regards to overall dysarthria severity, general rate of speech and the functional measure of communicative efficiency. The second group are characterized by significantly reduced pitch variation, reduced phrase length, reduced breath support for speech and increased hypernasality and features reflective of velopharyngeal incompetence. In contrast, the third subgroup features increased strain strangled vocal quality with a low rating for hypernasality. These features reflect a disturbance to the laryngeal mechanism and perceptually manifest in reduced vocal quality (15).

As speech deteriorates in quality, consequences can extend beyond the physiological impairment level and lead to activity limitation (for example difficulty communicating over the telephone) and can be influenced by key environmental factors (for example difficulty communicating in a noisy environment).

As well as motor speech difficulties, individuals with FRDA may present with other changes impacting on their overall communication. The impact of possible cognitive changes on communication may include difficulties generating ideas, planning and organizing messages and making inferences from spoken/written information; processing verbal information at speed (though see 2.14). Auditory processing skills may also be adversely affected in FRDA with one study identifying difficulties with understanding speech in background noise, despite normal performance on sound-detection audiograms (75) (see section 2.13).

2.7.2 Literature review of natural history of the speech disorder associated with Friedreich ataxia

Dysarthria (speech disorder) is a primary feature of FRDA, with estimates of prevalence ranging from 91% (59) to 100% (15, 69, 229). Earlier work by Harding (58) showed dysarthria to be present in all participants within 10 years of onset, suggesting that speech disorder is an inevitable outcome of disease progression. Dysarthria severity is known to be correlated with disease duration and overall disease severity as measured by the FARS score. This relationship suggests that the severity of dysarthria increases with increased disease duration (15).

2.7.3 Current assessment/investigations of speech in Friedreich ataxia

Evaluation of speech should be considered a key component of any assessment protocol for FRDA. Each individual should undergo a comprehensive speech assessment battery with a Speech and Language Pathologist (SLP) at the time of diagnosis or when symptoms or signs of speech disturbance first become apparent. Testing should be standardized using assessments psychometrically appropriate for monitoring change over time (e.g., not susceptible to practice effects). In some centers, standardized annual monitoring by the SLP may be provided whilst in others, there may be a responsive model, depending on the person's need. Needs of the individual with FRDA may be determined by change in circumstance e.g. transition from education to working environment; change of home environment, or by change in impairment level. There should be a clear pathway to enable individuals with FRDA to re-access the SLP.

The full examination (initial) should be designed to assess the communicative competence of individuals at impairment, activity and participation levels (International Classification of Functioning, Disability and Health, World Health Organisation, 2001(230)) and could include the following:

1. Oral motor examination.
2. Intelligibility assessment e.g. Assessment of Intelligibility of Dysarthria Speech ASSIDS (231).
3. Perceptual assessment of speech (e.g. Mayo Protocol) examining stress, rate, breathing pattern, loudness and pitch (232) and including diagnostic probing (e.g., maximum phonation time, pitch range). One standardized assessment, the Frenchay Dysarthria Assessment, has been shown to correlate significantly with FRDA progression as measured by the SARA score (233).
4. Perceptual assessment of voice e.g., Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V) (234), Grade, Roughness, Breathiness, Asthenia, Strain (GRBAS) (235).

5. Acoustic analysis of voice and prosodic features (e.g., noise to harmonics ratio, percent voicing in set phrases) – requiring recorded sample.
6. Assessment of voice and speech related quality of life e.g. Voice Handicap Index (VHI) (236).
7. Self report by individual with FRDA (e.g., using visual analogue scales).

These data will provide baseline information on which to rate performance in subsequent assessments and to devise individual management or intervention plans. Follow-up assessments can utilize relevant elements of the baseline protocol.

2.7.4 Current interventions/management of speech in Friedreich ataxia

Behavioral management is currently the primary management option available to individuals with FRDA with speech changes. Behavioral management is based on the assessment findings at the impairment level and incorporating the patient's life-role and wishes into treatment goals. It can include improving the underlying physiologic support for speech (e.g., improving trunk stability and breath support), modifying speech through compensatory speaking strategies (e.g., segmenting phrases and controlling rate to improve articulatory accuracy (16)), developing alternative and augmentative modes of communicating (e.g., text to voice software), and managing the communication environment (e.g., reducing background noise levels when speaking, conversation partner training). It is often beneficial to work jointly with colleagues from the multi-disciplinary team e.g. physical therapists for trunk stability and occupational therapists for accessing augmentative communication devices.

For patients presenting with a concomitant voice disorder, education on vocal hygiene (e.g., ensuring adequate hydration, consideration of diet) as well as general vocal health (e.g., avoiding phonotraumatic behaviors like throat clearing) and reducing muscular tension associated with the laryngeal mechanism may be beneficial.

Impairment-based therapy should adhere to principles of motor learning and neural plasticity (237). This means therapy needs to be goal driven, delivered on a regular basis, utilize extensive practice, incorporate multiple and varied tasks, integrate easily understood feedback, and involve communication partners. Adherence to these principles may aid the introduction and generalization of target behaviors (237).

A systematic evidence based program like the Lee Silverman Voice Technique (LSVT) has been shown to be effective in other degenerative disorders (e.g., Parkinson disease) with regards to speech impairment (238). LSVT has been shown to increase breath support, pitch range and vocal strength. Benefits of this approach in a single case study for acquired ataxic dysarthria have been documented (239) but no specific evidence exists for FRDA.

Interventions to improve the performance of listeners (i.e. communication partners of speakers with ataxia) might also be considered, including introduction of topic knowledge to improve comprehensibility (240) or familiarizing listeners with the characteristics of the speech-signal for the individual speaker (241).

If auditory processing deficits are identified, SLP communication training to the individual and key communication partners may be of use. Rance and colleagues (242) suggest training lip-reading and listening strategies and consider the use of radio-frequency listening devices. Support from audiologists should be considered.

Education should be available from the SLP about the nature of speech and communication changes in FRDA and to assist patients in recognizing and monitoring their symptoms.

2.7.5 Critical appraisal of the literature

There is currently no empirically documented population specific evidence on the benefit of speech therapy for individuals with FRDA. The evidence for the suggested therapies are based on diseases and disorders similar, but distinct from FRDA and need to be evaluated. The likely presence of speech impairment in all individuals with FRDA necessitates the urgent development and evaluation of effective and proven therapies for ameliorating this aspect of the disorder.

2.7.6 Recommendations

Recommendations	Grading
People with FRDA should undergo a comprehensive communication evaluation by a speech and language pathologist at the time of diagnosis or symptom onset and thereafter undertake review assessments to monitor performance.	C (15)
Instruction in environmental modification may be beneficial for individuals with motor speech difficulties.	C (16)
Participation in intensive and systematic behavior therapy may be beneficial to people with FRDA.	C (16)
Traditional non-systematic behavioral therapy may not be helpful for mitigating the effects of progressive dysarthria.	GPP

2.8 Dysphagia

Authors: Dr Adam Vogel*, Ms Melissa Loucas*, Ms Lucy Rodriguez, Dr Paola Giunti (*These authors have contributed equally)

2.8.1 Overview

Swallowing difficulties (oro-pharyngeal dysphagia) are a common symptom of Friedreich ataxia (FRDA). Dysphagia manifests in difficulties safely consuming foods and liquids and can result in a series of deleterious health and social consequences including extended meal times, reduced nutritional intake, restricted dietary options, social isolation, and aspiration (matter entering the lungs) potentially leading to pneumonia and death (243).

2.8.2 Literature review of natural history of swallowing difficulties in Friedreich ataxia

Data on the nature and progression of swallowing difficulties in people with FRDA is extremely limited. No longitudinal studies exist documenting the onset, nature or progression of dysphagia in FRDA and no studies have formally characterized the swallowing deficits presenting in this population. An inverse relationship with GAA1 repeat length has been found for onset of dysphagia (69), however the link between dysphagia severity and size of repeat was not reported. Dürr and colleagues (59) found that swallowing difficulties were associated with disease duration alone. There is some evidence, based on a broad ataxia rating scale, suggesting that approximately 7% of individuals present with dysphagia when classified in the earlier stages of the Inherited Ataxia Progression Scale modified for FRDA (IAPS), stages I and II, with increases to 21 and 53% for IAPS stages III and IV respectively (72). Anecdotal evidence suggests that dysphagia appears with advancing disease and people with very advanced disease frequently choke, requiring modified foods and eventually nasogastric tube or gastrostomy feeding (244). As well as coughing or choking on food and/or drink, other dysphagia symptoms include difficulties controlling food or drink in the mouth, chewing difficulties, drooling, nasal regurgitation and a sensation of food lodging in the throat. Nilsson and colleague's (245) small study of individuals with hereditary sensory ataxia (including two people with FRDA) described no spontaneous self-report of dysphagia but a number of pharyngeal and oesophageal symptoms on direct questioning. Swallowing difficulties may be exacerbated when there are coexisting postural or hand-to-mouth coordination difficulties.

2.8.3 Literature review of current assessment/investigations

Given the importance of adequate nutrition, swallow function should be considered a key component of any assessment protocol for individuals with FRDA when dysphagia symptoms are reported or signs are identified during medical review. Each individual reporting symptoms on questioning or showing signs of dysphagia should undergo a

comprehensive swallowing assessment by a Speech and Language Pathologist (SLP) and receive intervention and monitoring as appropriate. Re-assessment may be initiated by the individual reporting progression of symptoms or by another member of the multidisciplinary team (MDT).

The full dysphagia examination should be designed to assess the swallowing competence of each individual in terms of physiological impairment and impact on activity and participation. As a minimum, assessment should include the following:

3.1.4.1 Enquiry about symptoms of dysphagia, current diet, mealtime behaviors, absence/presence of chest infections, history of weight loss.

3.1.4.2 Oral-motor examination.

3.1.4.3 Clinical bedside examination of swallow as appropriate to presenting signs and symptoms. This may include trials of normal consistencies of food and fluid, and modified textures e.g., puree or thickened fluids.

3.1.4.4 Quality of life measures specific to dysphagia (e.g., SWAL-QOL (246)).

Fluoroscopic evaluation of swallow is an instrumental assessment which provides a more detailed and objective description of the oral and pharyngeal components of swallowing function. Fluoroscopic evaluation of the swallow is used when there is insufficient information at the bedside assessment to describe the presenting dysphagia and/or to guide management. The assessment itself may follow a standardized procedure e.g., Bethlehem Swallowing Assessment (18) and/or utilize published scales to describe videofluoroscopic swallowing study (VFSS) events e.g. Penetration-Aspiration Scale (17).

A comprehensive assessment guides the individually specific management plan. It also provides baseline information against which to rate performance on subsequent assessments.

Follow-up assessments are important to track swallow deterioration and inform amendment of management plans. These should be timely and responsive to any change and therefore access to SLP review should be facilitated by the MDT and supported by policy agreements around open access for patients with long-term progressive conditions. Individuals with FRDA and their caregivers/family should be informed about indicators of a worsening swallow in order to initiate informed requests for swallow review as needed.

2.8.4 Literature review of current interventions/management

Management of swallowing difficulties in FRDA is aimed at facilitating safe and adequate nutrition and hydration. Intervention may be beneficial at any stage during disease progression and is likely to alter over time according to patient need. In people with mild dysphagic symptoms or who have been recently diagnosed, the focus may be on

giving information regarding the potential symptoms of dysphagia and the role of SLP in supporting swallowing difficulties. As symptoms and clinical signs become more prominent, specific therapeutic exercises and strategies should be considered. These include environmental modifications, such as reducing distractions and promoting focus on the task of swallowing e.g. eliminating talking during meals.

Postural modification can improve swallowing efficiency and safety. Clinicians need to identify the body position that enables optimum swallow function for the individual. This is usually a comfortable and stable position. Collaboration with colleagues in physical therapy and occupational therapy is recommended, particularly where individuals may need support or specialist seating systems.

Compensatory head postures have been shown to improve swallow function in other neurological conditions including dementia and Parkinson disease. In particular, adopting the chin down posture has been shown to alter oro-pharyngeal dimensions (20) and in some small studies resulted in improved swallowing in some cases by reducing the depth of laryngeal penetration and residue (21) or reducing aspiration (22).

In other neurodegenerative conditions, altering bolus size and viscosity has been shown to affect swallow characteristics, with increasing bolus viscosity significantly improving safety and efficacy of swallowing (24). Similarly, increased bolus volume severely impaired the safety and efficacy of swallowing (24). The equipment used when eating and drinking can also alter an individual's swallowing safety and efficiency. Controlled flow drinking containers allow the user to limit the rate and amount of fluid entering their mouth at any one time. For some individuals where hand-mouth in-coordination affects the ability to control the size of a fluid bolus, use of a narrow bore straw may be beneficial. However, the individual needs to be assessed for their ability to control suction and bolus size, as rapid sequential drinking through the straw may increase episodes of aspiration (247). Consultation with Occupational Therapy is recommended in investigation of aids or adaptations to optimize delivery of food and drink to the mouth.

Dietary modification is another management option available. It involves altering the diet of an individual to exclude or modify textures and consistencies identified as being problematic for the individual e.g. causing coughing or choking. These may include dry crumbly foods (e.g., biscuits, nuts), small, easily inhaled foods (e.g., desiccated coconut, sesame seeds) and foods which are difficult to chew/breakdown (e.g., steak, apple). Preliminary evidence in related populations (e.g., geriatric) suggests patients can increase body weight via a diversified and appealing diet, modified in texture that meets their nutrition needs (23). Modification of fluid viscosity has also been shown to reduce adverse swallowing events such as aspiration in some patients with other neurodegenerative conditions (21, 24). The importance of dietary modification and

dysphagia management necessitates a close working relationship with a dietician to ensure optimal nutrition and hydration.

The use of early behavioral swallowing intervention incorporated into standardized programs of therapy, including dietary modification, has led to more favorable outcomes in stroke patients (19) as well as people with dementia and Parkinson disease (21). Until a stronger body of evidence is established for the treatment of dysphagia in individuals with FRDA, behavioral techniques used with appropriate populations should be considered. For example, effortful swallows have been shown to decrease oral residue in healthy adults (248).

More invasive interventions are also available for individuals with significant issues relating to nutrition or hydration and swallowing safety. Supplementary feeding techniques (e.g., nasogastric or gastrostomy tube feeding), provide a means for increasing nutritional intake by a non-oral route. These methods are often effective in weight maintenance/gain and may reduce aspiration episodes (aside from secretions), however they can be limited by potential complications including chemical peritonitis, infection, bowel perforation, hemorrhage and altered lifestyle (249). It is important to consider such techniques as supplementary to oral feeding rather than alternatives, with the aim of intervention to continue oral feeding (modified as necessary) in order to offer the best quality of life possible (250). Any such interventions should be managed within a multidisciplinary team and patient informed consent is fundamental.

As upper limb motor difficulties may impact on the ability of people with FRDA to self-feed, SLP management should also encompass training and education of family members or care-givers. Compliance of care-givers with advice on feeding has been shown to increase when SLP training is given (251).

As with management of other long term conditions, the wishes of the patient are central to management and need to be respected. The multidisciplinary team has a duty to ensure that individuals with FRDA are provided with relevant information so they can make informed decisions about their own care. Dysphagia education is vital to provide patients with options for management of any difficulties that arise. Ensuring individuals with FRDA enjoy a relatively high quality of life should be a primary concern for all those working with individuals with FRDA and respecting an informed choice to refuse treatment may play a role in maintaining that quality.

2.8.5 Critical appraisal of current literature

There is currently no empirically documented population specific evidence on the benefit of swallowing therapy of individuals with FRDA. The evidence for the suggested therapies are based on diseases and disorders similar, but distinct from FRDA and need to be evaluated. The likely presence of dysphagia in all individuals with a FRDA

necessitates the urgent development and evaluation of effective and proven therapies for ameliorating this aspect of the disorder.

2.8.6 Recommendations

Health professionals need to ensure individuals with FRDA have access to information and education about possible swallow changes as a result of disease progression.

Individuals with FRDA require comprehensive and timely assessments and reviews of swallow function by speech pathologists.

Individual management plans should be developed from assessment findings. Interventions may utilize strategies shown to be of benefit in other neurological conditions, including postural, environmental, and dietary modification and behavioral techniques.

Augmentative and alternative feeding options should be discussed with the individual, their family and the multidisciplinary team in a timely manner.

Recommendations	**Grading**
People with FRDA should undergo a comprehensive swallowing evaluation by a speech and language pathologist at the time of diagnosis or symptom onset and thereafter to monitor performance.	D (17, 18)
Instruction in environmental modification and compensatory postures may be beneficial for individuals with dysphagia.	D (19-22)
Instruction in dietary modification may be beneficial for individuals with dysphagia.	D (21, 23, 24)
Traditional non-systematic behavioral therapy (e.g., oral motor therapy) may not be helpful for mitigating the effects of dysphagia.	GPP

2.9 Vision

Authors: Professor David R. Lynch; Ms Lauren Seyer; Dr Laura Balcer.

2.9.1 Overview

Both afferent and efferent visual abnormalities may be found in individuals with FRDA. Oculomotor findings associated with FRDA include optic atrophy, square wave jerks, and difficulty with fixation (74, 252). Most people with FRDA have normal high-contrast visual acuities, but a subpopulation has mildly decreased high contrast visual acuity, usually not worse than 20/30. On the other hand, people with FRDA have significantly worse low-contrast visual acuity a hallmark of optic atrophy, as compared to controls (253). Clinical or subclinical optic neuropathy is found in approximately two-thirds of people with FRDA, although severe visual loss is uncommon (254). While most individuals with FRDA have a degree of visual field dysfunction, visual field defects range from severe visual field impairment to only isolated regions of reduced sensitivity, as measured by optical coherence tomography (OCT). Therefore, optic nerve involvement and axonal loss most likely begins early in the condition and slowly progresses to the point of clinical involvement. However, a few individuals have rapid system dysfunction, similar to that observed in other mitochondrial diseases such as Leber hereditary optic neuropathy (LHON) (73, 255). This may be more commonly identified in people who are heterozygous for a point mutation on one allele and a GAA repeat expansion on the other, rather than being homozygous for expanded *FXN* alleles, although there is little systematic evidence for this conclusion and rapidly progressive optic neuropathy has been noted in people carrying two expanded GAA repeats.

Visual abilities have been measured both functionally using techniques such as low contrast letter acuity (253) and more recently anatomically using OCT (254, 256). OCT is a non-invasive, high resolution technique that quantifies the thickness of ocular structures, particularly the retinal nerve fiber layer, and can generate a complete picture of anatomic structure of the retina. OCT has recently demonstrated that a significant number of people with FRDA have thinning of the retinal nerve fiber layer (256). However, this thinning is not always clearly reflected in overt visual dysfunction (as measured by visual acuity testing), suggesting that not all retinal abnormalities manifest clinically.

2.9.2 Literature review of visual function in Friedreich ataxia

2.9.2.1 Affected population

Individuals with FRDA classified as having “classical” or late-onset forms of the disease can all experience loss in visual function. The loss of visual function, as tested using low-contrast visual acuity, correlates with poorer scores on neurologic exams such as FARS

(253). Therefore, more severely affected individuals are also more likely to develop decreased visual acuity. The loss of visual function is not as strongly associated with age of onset; thus, individuals with symptom onset at any age can develop vision loss at later stages of disease progression.

2.9.2.2 Current investigation/intervention/treatment options

There are currently no treatment options to address specific components of visual loss or the anatomic thinning of the retina or macula. Currently, individuals with myopia, hyperopia, astigmatism, and other such visual abnormalities (which do not have increased incidence in FRDA) are treated using standard refractive correction such as glasses, contact lenses, and Lasik surgery. Square wave jerks do not normally cause difficulties with vision and are not treated.

There are no treatments specifically targeted toward improving visual function abnormalities in FRDA.

2.9.3 Efferent visual function (eye movement features) in Friedreich ataxia

Efferent visual function is less commonly discussed in FRDA, perhaps because they contribute less to dysfunction. They include primarily fixation abnormalities (ocular flutter, square wave jerks), and to a lesser extent nystagmus or saccadic abnormalities. These are all traditionally diagnostic features but have less need for therapy in the overall context of the disorder. Despite 20:20 vision people with FRDA may report reduced visual quality of life as reported by Fahey and colleagues (74).

2.9.4 Literature review regarding current investigation/ intervention/ treatment options

There are no approved treatments for square wave jerks or ocular flutter, particularly given the relative lack of symptomatology in FRDA compared to other disease manifestations. In other disorders, Memantine, Acetazolamide, Aminopyridine, Clonazepam, Gabapentin and Ondansetron have been suggested to have benefit (25).

At present guidelines reflect the same need for visual screening as in afferent function, with attempted treatment of symptoms as needed.

2.9.5 Recommendations

There are currently no formal guidelines or recommendations for screening/diagnosis of optic atrophy or visual dysfunction in FRDA. As a small percentage of individuals with FRDA develop loss of vision, screening or testing beyond the guidelines used by the

general public may not be necessary. That being said, it may be helpful to individuals with FRDA to understand the visual symptoms that may occur as a consequence of FRDA, despite the fact there is limited treatment available for visual disorders.

General vision screening recommendations specific to the country in which the person with FRDA is being treated should be followed. In cases of diabetes in FRDA or family history of eye disease/diabetes, or if the person experiences symptoms of pain or unusual vision patterns, they are encouraged to see an ophthalmologist more frequently or as soon as possible depending on the symptoms experienced or the case involved.

Recommendations	**Grade**
Screening or testing as per country specific general vision screening guidelines should be applied to individuals with FRDA.	GPP
Memantine, Acetazolamide, Aminopyridine, Clonazepam, Gabapentin or Ondansetron may be of benefit in treating square wave jerks and ocular flutter.	D (25)

2.10 Bladder Function

Authors: **Dr Paola Giunti, Dr Jalesh Panicker, Dr Anton Emmanuel, Dr Marios Hadjivassiliou**

2.10.1 Overview

From the limited data available, bladder symptoms appear to be a common problem in people with FRDA. Delatycki and colleagues observed that 41% of a cohort of individuals with FRDA from eastern Australia with homozygous *FXN* intron 1 GAA expansions reported bladder symptoms and this did not correlate with the size of the gene mutation (57). Dürr and colleagues noted a prevalence of 23% in their cohort of 140 people (59).

Information about the pattern of bladder dysfunction in individuals with FRDA is sparse. It has been established that symptoms tend to correlate with disease duration (57). Vezina and colleagues observed that individuals with FRDA most often reported overactive bladder symptoms, with urgency incontinence being the commonest (257). The problem is made worse when mobility is affected and it is difficult to reach and transfer to the toilet in time. More recent data derived from the Collaborative Clinical Research Network (CCRN) in FRDA sheds light into the extent of bladder troubles. Amongst 578 individuals included in this database, urgency was reported in 31% and incontinence in 27%. Ninety-one (16%) people reported frequent urinary incontinence (greater than once a week), amongst whom two required catheterization and 28% reported that bladder problems had altered their activities. However, only 13% were on medications for bladder symptoms (Cooperative Clinical Research Network in Friedreich Ataxia, J Farmer, D Lynch, and A Brocht, unpublished observations).

Bladder overactivity is the most common component of bladder dysfunction in FRDA. This is a result of the bladder contracting unpredictably and sometimes uncontrollably. Urodynamic studies demonstrate a variety of changes including uninhibited contractions and altered bladder capacity (257, 258). These changes presumably reflect pyramidal tract involvement in FRDA (12). The commonest finding in needle EMG of the external urethral sphincter is complete voluntary relaxation (257).

2.10.2 Review of the literature on managing bladder dysfunction in Friedreich ataxia

An extensive literature search did not uncover any publications that specifically addressed the management of bladder problems in FRDA. Therefore, the guidelines proposed are based on limited understanding of the pathophysiology of lower urinary tract dysfunction in individuals with FRDA mentioned in the above case series (level IV evidence). Management of urological issues in people with FRDA should be by a suitably trained health care professional who is knowledgeable about the ataxias and neurogenic lower urinary tract dysfunction. In the majority of cases, the bladder can be successfully

managed based upon a simple algorithm which has been adopted from treatment guidelines for bladder dysfunction in patients with multiple sclerosis (see figure 1.9.1) (27).

2.10.3 Evaluation of bladder dysfunction

The first step when evaluating urinary function in people with FRDA is to test for a urinary tract infection (UTI) (26, 27). UTIs can themselves worsen neurological symptoms (259).

The initial assessment should also include assessment of post micturition residual urine, preferably before antimuscarinic medications are started. This measurement can be made by either using ultrasound or catheterization. Urodynamic studies are not routinely performed unless bladder symptoms are refractory to treatment or intravesical treatment is being planned. Other urological/gynecological causes for bladder symptoms such as prostate enlargement or stress incontinence should be appropriately ruled out.

2.10.4 Treatment of bladder dysfunction in Friedreich ataxia

The algorithm in figure 2 outlines the management of bladder dysfunction. Practical advice should be given about cutting down caffeine, fizzy drinks and alcohol, as well as information about timed voiding and bladder retraining whenever appropriate. The fluid intake should be individualized, particularly taking into consideration possible concurrent cardiac issues, however a fluid intake of between 1 to 2 litres a day is recommended (27). Pelvic floor exercises may be helpful especially when symptoms are mild.

Most individuals with FRDA and overactive bladder symptoms will require antimuscarinic medications (see Table 3 for a list of medications). The most often experienced side-effects are dry mouth and constipation. If the former is too uncomfortable, then artificial saliva may be prescribed, in either tablet or spray form. Antimuscarinic medications can increase heart rate, which may be relevant in a patient with cardiomyopathy. Cognitive problems can occur in FRDA (12) and in the rare situation where cognitive impairment is a feature; antimuscarinics should be prescribed with caution. In this setting it would be sensible to use more selectively-acting medications such as trospium or darifenacin. If symptoms continue to be refractory, intradetrusor injections of botulinum toxin A is an option.

From the review of literature, voiding dysfunction and incomplete bladder emptying occur only rarely in people with FRDA. In individuals with persistently elevated post void residual volumes in excess of 100 mL, clean intermittent self-catheterisation (CISC) is indicated. This should be taught by a urology specialist nurse or continence advisor.

However manual dexterity and vision need to be assessed when considering CISC. With advancing disease, an indwelling catheter, preferably supra-pubic, may be necessary.

Referral to specialist urology services is indicated in case of haematuria, suspicion of concomitant urological condition, e.g. prostatic enlargement, frequent urinary tract infections and symptoms refractory to medical management. It should also be done for consideration for intradetrusor injections of botulinum toxin A or need for CISC or suprapubic catheterization.

2.10.5 Recommendations for management of bladder dysfunction

Recommendations	Grading
Exclusion of a concomitant urinary tract infection and assessment of post micturition residual urine is recommended prior to commencement of treatment.	C (26, 27)
Antimuscarinic medications may be considered for people with FRDA displaying overactive bladder symptoms.	GPP
Intradetrusor injections of Botulinum toxin A or suprapubic catheterization may be considered as alternative intervention.	GPP
In a patient with persistently elevated post void residual volumes in excess of 100 mL, clean intermittent self-catheterization is indicated.	GPP

Table 5 Antimuscarinic medications that can be used to manage overactive bladder symptoms.

Generic name	Trade Name	Dose (mg)	Frequency
Propantheline	Pro-Banthine	15	tds
Tolterodine tartrate	Detrusitol	2	bd
Tolterodine tartrate	Detrusitol XL	4	od
Trospium chloride	Regurin	20	bd
Oxybutynin chloride	Ditropan	2.5 - 5	bd - qds
Oxybutynin chloride XL	Lyrinel XL	5 - 30	od
Propiverine hydrochloride	Detrunorm	15	od - qds
Darifenacin	Emselex	7.5 - 15	od
Solifenacin	Vesicare	5 - 10	od
Fesoterodine	Toviaz	4-8	od

Reproduced from Journal of Neurology Neurosurgery and Psychiatry. With permission from Fowler, Panicker, Drake, and colleagues (27)

Legend: od – once daily; bd – twice daily; tds –three times daily; qds – four times daily, XL – extended life

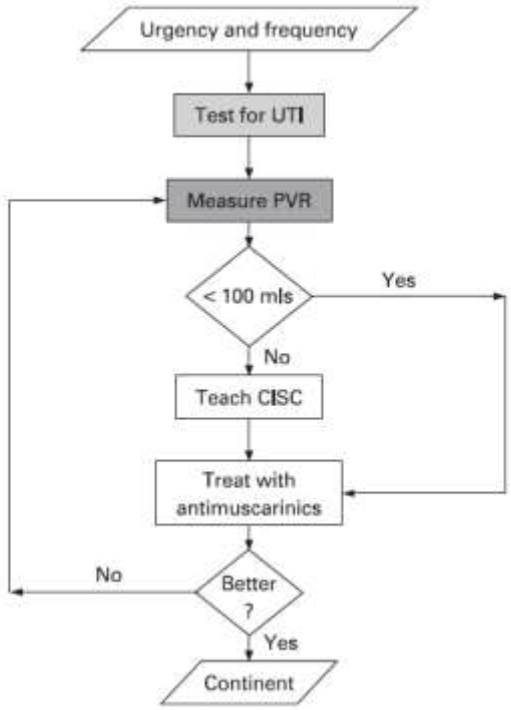

Figure 2 Algorithm for managing bladder symptoms in Friedreich ataxia Reproduced from Fowler, Panicker, Drake, and colleagues (27) with permission from Journal of Neurology Neurosurgery and Psychiatry
Legend: CISC = clean intermittent self-catheterization; PVR = post-void residual urine

2.11 Bowel Function

Authors: Dr Paola Giunti, Dr Jalesh Panicker, Dr Anton Emmanuel, Dr Marios Hadjivassiliou.

2.11.1 Overview

Symptoms of bowel dysfunction are common in individuals with neurological disease, and the clinical impression is that this is no different amongst individuals with FRDA **(260)**. Symptoms including constipation and faecal incontinence are also prevalent in the general population (261, 262). Constipation is present in 11% of the healthy population, and faecal incontinence in 2%. It is anticipated there is increased prevalence of bowel dysfunction in FRDA over and above the figures in the healthy population however there are no published studies on this. There is a need for further controlled data on bowel dysfunction in FRDA.

The spinal neurodegeneration of FRDA would be expected to result in gut symptomatology, in an analogous way to the symptoms that develop in patients with spinal cord injury (260). The etiology of these symptoms is complex; there may be autonomic and pelvic nerve dysfunction (with attenuation of voluntary motor function and impaired anorectal sensation and anorectal reflexes), or generalized systemic factors (e.g., altered diet and behavior, impaired mobility, psychological disturbances or drug adverse effects) (263). The mainstay of current treatment is adopting a conservative approach and optimizing the mechanics of defecation through the use of laxatives and irrigation approaches (264). When successful, this approach improves both evacuation and incontinence symptoms, with associated improvements in quality of life and independence. Future therapies may be directed at modulating pelvic innervation through electrical stimulation.

2.11.2 Conclusion

Bowel symptoms in FRDA are frequently reported. Evaluation of bowel function should form part of the routine care of an individual with FRDA. Currently the etiology underlying reported bowel dysfunction is not clear. Studies aiming at understanding the pathophysiology of bowel symptoms in FRDA are urgently needed. The recommendations outlined here are based on experience and data from similar but distinct conditions. Studies evaluating the management of bowel dysfunction in people with FRDA would strengthen any recommendations.

2.11.3 Recommendations for management of bowel dysfunction

Recommendations	Grading
Consider modifying diet and lifestyle to optimize stool consistency and avoid fecal incontinence.	GPP
Titrate appropriate laxatives to optimize gut transit, stool consistency and avoid fecal impaction. Consider the use of prokinetic drugs.	GPP
Avoid fecal incontinence by treating fecal impaction if present. Facilitate prompt rectal evacuation via use of manual manoeuvres, use of suppositories/mini enemas. Consider use of transanal irrigation and biofeedback behavioral therapy.	GPP

2.12 Sexual Function

Authors: Dr Paola Giunti, Dr Jalesh Panicker, Dr Anton Emmanuel, Dr Louise Corben, Dr Marios Hadjivassiliou.

2.12.1 Overview

Sexual dysfunction including erectile dysfunction and altered genitosensory capacity may occur in individuals with FRDA as with many people with neurological conditions (265). An understanding of the pathophysiology of the sexual response and the role of the sexual response in the health, well-being and quality of life is essential for all clinicians working with people with progressive neurological disorders such as FRDA. The sexual response is a complex phenomenon and in people with FRDA may well be influenced by multiple factors including the function of neurological, cardiac or vascular systems; attitudes towards sexuality or the individual's self-esteem or self-worth (265) (see (266) for details regarding physiology and anatomy of sexual response).

Sexual dysfunction in people with neurological conditions can be devastating (265). It is essential the clinician does not ignore this fundamental aspect of a person's life. In particular it is important the clinician establishes the presence and in so doing, clarifies the nature, history and characteristics of any sexual dysfunction. This should include details of libido, genital sensation, erectile function, lubrication, ejaculation, orgasm and menstrual function. A clinical examination and investigations may also be indicated (266). The effect of concurrent conditions such as depression and medication such as SSRIs and antihypertensives should also be explored (266, 267).

2.12.2 Addressing issues related to sexual dysfunction in Friedreich ataxia.

As reported in like conditions such as multiple sclerosis individuals with FRDA should be encouraged to discuss sexual function in the clinical setting (267, 268). In particular people with FRDA particularly in the latter stages of the disease process, may have physical impairments that make sexual function difficult. Referral to sexual counseling or exploration of alternative and practical methods of sexual expression may be appropriate (267, 268). Practical suggestions may include alternative positions, use of lubrication or use of sex aids (265). In addition counseling to address issues such as reduced self-esteem or self-worth is vital to ensuring healthy sexual function (266, 268).

Erectile dysfunction should be treated symptomatically with phosphodiesterase-5 inhibitors, i.e., Sildenafil, Tadalafil and Vardenafil if not contraindicated by concomitant cardiac symptoms. Treatment goals should be balanced between the needs of the person and potential side effects including cardiac impact.

The role of hormone insufficiency in women reporting reduced sexual arousal or desire in women may be investigated. Use of hormone replacement therapy may be explored in post-menopausal women (266)

2.12.3 Conclusion

Sexual dysfunction in individuals with FRDA can have a profound effect on quality of life. Evaluation of sexual function should form part of the routine care of an individual with FRDA. Currently the etiology underlying reported sexual dysfunction is not clear. Studies aiming at understanding the pathophysiology of sexual dysfunction in FRDA are urgently needed.

2.12.3 Recommendations for management of sexual function in Friedreich ataxia

Recommendations	**Grading**
Individuals with FRDA may benefit from discussion regarding their sexual function.	GPP
Reported sexual dysfunction should be investigated.	GPP
Symptomatic management of erectile dysfunction involves the use of phosphodiesterase-5 inhibitors, e.g. Sildenafil, Tadalafil and Vardenafil but should only be prescribed in an individual with cardiac disease after consultation with the individual's cardiologist.	GPP

2.13 Audiological function

Authors: Associate Professor Gary Rance, Dr Thierry Morlet

2.13.1 Overview

Auditory pathway abnormality is a consistently reported feature of FRDA. While sound detection is typically normal or near-normal (58, 59, 242), almost 100% of individuals with FRDA (will eventually) show evidence of disordered neural conduction in the central auditory pathways and abnormal perception of complex signals (including speech).

Peripheral auditory function (that is the physiology of the middle and inner ear) is generally unaffected in individuals with FRDA, but neural activity is abnormal. Electrophysiologic assessment typically reveals absent or distorted potentials from the cochlear nerve and auditory brainstem (242, 269, 270) in conjunction with normal pre-neural responses from the cochlear (outer) hair cells such as otoacoustic emissions and cochlear microphonics (242, 271, 272). This result pattern is consistent with histological evidence showing preserved cochlear structures (organ of corti and hair cells) and selective cochlear nerve damage (273).

The perceptual effects of auditory pathway disorder in listeners with FRDA are distinct from those caused by peripheral hearing loss. Whereas cochlear damage results in impaired sound detection thresholds and distortion of pitch perception, the neural dys-synchrony associated with FRDA results in disruption of temporal (timing) cues (242).

The functional consequences of this temporal distortion are often severe with almost all FRDA listeners showing impaired speech understanding in background noise (28, 242) and reporting impaired communication ability in everyday circumstances (30), which worsens with the progression of the disorder.

2.13.2 Literature review of natural history of audiological dysfunction in Friedreich ataxia.

There are currently no published longitudinal data tracking auditory pathway changes in individuals with FRDA. Cross-sectional studies have, however, shown correlations between overall disease severity (as measured by the Friedreich Ataxia Rating Scale [FARS]) and auditory temporal processing (28) and between FARS score and speech perception (28, 30, 242).

2.13.3 Current investigation for audiological dysfunction in Friedreich ataxia

Assessment of auditory function should form part of the standard FRDA management protocol. Each individual should undergo a comprehensive auditory evaluation at the time of diagnosis and then have a hearing screen on an annual basis, or sooner if warranted by a sudden change in auditory performance.

The full (initial) evaluation should assess both peripheral function and the central auditory pathways and include the following:

1. Sound detection thresholds (audiogram)
2. Speech perception (in quiet and background noise)
3. Auditory evoked potentials (auditory brainstem response (ABR)/cochlear microphonic using both condensation and rarefaction stimuli)
4. Otoacoustic emissions (OAE)
5. Hearing disability survey

Findings from the above can form a baseline measure of auditory function and a basis for intervention (if required).

Annual follow-up evaluations should include at least the following:

1. Middle ear muscle reflex (if thresholds are absent or elevated, check ABR)
2. OAE
3. Speech perception in quiet and in noise

2.13.4 Literature review of intervention for audiological dysfunction in Friedreich ataxia

Instruction in "listening tactics" can be beneficial for all individuals with hearing difficulties (29). The aim of these strategies is to help the listener optimize social interaction by controlling the communication environment. This may involve a range of measures including minimization of background noise and maximization of visual (lipreading) cues.

Conventional hearing aids tend not to be useful in listeners with FRDA as they are designed to make sounds louder (which is typically not required for this population) and do not overcome the neural distortion typically associated with FRDA.

There is no evidence as to whether or not cochlear implants help individuals with FRDA. One unsuccessful case of cochlear implantation in a patient with a clinical diagnosis of FRDA is reported in the literature (274). However, this individual had profound hearing loss and was legally blind by the age of 10, which is rare in FRDA, and the paper does not mention that genetic testing was done to confirm the diagnosis. Thus, this case is not typical of FRDA. Regardless, the option of a cochlear implant needs to be discussed with FRDA patients who are having hearing difficulties.

FM-listening devices, in contrast, can improve day-to-day listening and general communication in individuals with FRDA (30). These systems transmit speech signals (detected by a lapel microphone worn by the speaker) via radio-waves to ear level receivers worn by the listener. As such, they improve access to the signal because the speech is louder (relative to the background noise) at the listener's ear.

2.13.5 Affected patient population

Auditory deficits have been identified in FRDA patient populations with both pediatric and adult onset (30). All of the above-mentioned assessment techniques are suitable for subjects aged 5 years and above.

Listening tactics tend to be difficult for children to implement, but FM-devices are specifically designed for structured listening situations (such as the classroom) and can be fitted from infancy.

The above-described recommendations are supported by Level III-2 evidence from a series of case-control studies (28, 30, 242).

2.13.6 Evidence for recommendations

The evidence for benefit from FM-device fitting is the weakest (at this stage). Two potential limitations need to be mentioned:

1. Listener headsets have been made as small as possible, for cosmetic reasons. This can create problems for users with fine motor problems.
2. The device is designed to improve communication between a primary speaker (e.g. a teacher) and the listener. Thus, the system works well for children and one-on-one interactions, but has limited application for adults in group situations.

<u>FM-Device</u>
Benefit: It significantly improves day-to-day communication (30)
Side effect: It is a potential source of unwanted attention because the user needs to wear a headset.

An FM-system must be fitted by an audiologist. Thus, audiological support is essential. For classroom use, the teacher must be willing to participate by wearing a lapel microphone.

2.13.7 Recommendations

Recommendations	Grading
People with FRDA should undergo a comprehensive auditory evaluation at the time of diagnosis and thereafter annually undertake a hearing screen or sooner if warranted by a sudden change in auditory performance.	B (28)
Instruction in “listening tactics” may be beneficial for individuals with hearing difficulties.	B (29)
FM-listening devices fitted by an audiologist may improve day-to-day listening and general communication in individuals with FRDA.	B (30)
Conventional hearing aids and cochlear implants may not improve the hearing impairment related to FRDA.	GPP

2.14 Cognition

Authors: Dr Louise Corben, Professor Jörg Schulz

2.14.1 Overview

Traditionally, the cerebellum has been thought to coordinate voluntary movement and control of motor tone, posture and gait (275). Until recently documentation of cognitive function in FRDA was scarce, possibly because FRDA was widely held to predominantly affect the spinal cord, peripheral sensory nerves and cerebellum (276) and therefore not affect cognition. The last few decades has seen a significant shift from a cortico-centric view of cognitive function to a view that embraces the significant contribution of the cerebellum in cognitive, language and affective regulation (277-284). Accordingly there has been an associated interest in examining the effect of FRDA on cognitive development and function. This is important in order to characterize the cognitive behavioural profile associated with FRDA and develop interventions that ensure people with FRDA are able to maximize their potential in terms of cognitive function.

In addressing the sensitive issue of cognitive function in people with FRDA it should be noted that the deficits described thus far are quite specific in nature and generally such deficits do not preclude a person with FRDA from participating in education at school and college/university, gaining meaningful and at times cognitively demanding employment, partnering and raising a family. Understanding the heterogeneous nature of the cognitive changes related to FRDA and the mechanisms that underpin such changes is worthy of considerable ongoing research to ensure the impairments associated with FRDA do not dictate an individuals' capacity to participate in all aspects of life.

2.14.2. Literature review and natural history of cognitive changes in Friedreich ataxia

Early studies examining cognition in FRDA focused on psychiatric impairment (285, 286), speed of information processing (276, 287-290) and general cognitive function (291, 292). Slowed information processing was a consistent finding of these studies, whereas changes to other cognitive functions were not consistently reported. These earlier studies, while acknowledging the difficulty of dissociating a deficit in motor function from a cognitive deficit (293), were in general agreement that changes to cognitive function in people with FRDA were secondary to cerebellar pathology (see (294) for review).

More recently there has been an increment in studies aimed at understanding the neurobehavioral profile associated with FRDA, often utilizing traditional neuropsychological assessments incorporating tests of intelligence (295, 296, 297). Mantovan and colleagues (295) found that individuals with FRDA were, compared to

control participants, impaired in tasks related to visuoconstructive and visuoperceptual capacity, verbal fluency, motor and mental reaction times. Whilst these results did not represent a major impairment in intelligence, cognition of people with FRDA was found to be characterized by concrete thinking resulting in reduced concept formation and visuospatial reasoning (295). de Nóbrega and colleagues (296) also noted individuals with FRDA performed significantly more poorly on phonemic and action fluency tests when compared to control participants. More recently Nachbauer and colleagues utilized neuropsychological assessments to evaluate executive function, attention, memory and visual perception in 29 individuals with FRDA compared to control participants (298). In addition, outcomes measures for participants with FRDA were correlated with clinical parameters. On the basis of these assessments Nachbauer and colleagues reported cognitive impairment, apparent as attentional and executive dysfunction, affected only a subgroup of people with FRDA. Better cognitive performance was associated with shorter GAA repeat length, later disease onset and lesser disease severity (298).

The use of standardized assessments of intelligence in people with FRDA, whilst providing some information regarding intelligence per se, provides little understanding of the capacity of people with FRDA to manage a situation requiring flexible and comprehensive cognitive abilities. Individuals with FRDA often become quite physically impaired at a critical time of their neural development and education and may have a concurrent hearing impairment that if undetected in the school environment, may have an impact on the capacity to learn (28). Reduced performance on specific tests of intelligence may well reflect compromised educational opportunities rather than direct impairment (297, 299). Alternatively, as pointed out by Mantovan and colleagues (295), the neuropsychological and affective changes in people with FRDA may reflect primary cerebellar pathology. It is likely the observed changes may reflect a combination of both aspects (177, 300, 301).

The area of personality changes as a consequence of FRDA has received scant attention. The most significant though albeit small study was by Mantovan and colleagues (295) who administered the Minnesota Multiphasic Personality Inventory (MMPI) to eight participants with FRDA. Of these eight participants, half (n=4) returned personality profiles that were outside the normal range demonstrating increased irritability, poor impulse control and blunting of affect. Mantovan and colleagues (295) postulated these changes may be the consequence of the onset of symptomatology of FRDA in adolescence, a critical time for personality formation or perhaps the daily living and participatory restrictions imposed by the condition that provide a modifying influence on otherwise adaptive behavior or ultimately the condition itself. Either proposal or a combination of the three seems plausible and provides an interesting basis for future examination (295).

FRDA inherently presents as a disorder of movement. The most effective method to explore cognitive function is usually through the use of paradigms that assess reaction time (RT). Most studies previously reported have incorporated the use of RT. However, attempting to characterize cognitive function in FRDA utilizing RT may be confounded by the effect of FRDA on motor function. Corben and colleagues employed a number of studies to examine psychomotor function in people with FRDA whilst controlling for issues related to RT (222, 302, 303). These studies examined the capacity to respond to unexpected change in movement, to utilize advance information to plan movement, to generate a motoric response to incongruent stimuli and to accommodate changes in moving to targets differing in size and distance apart. Importantly each study correlated movement outcomes with clinical parameters. Individuals with FRDA had difficulty accommodating unexpected movement, were disadvantaged by conditions requiring initiation of movement without a direct visual cue and were differentially affected in reaction time to incongruent, compared with congruent stimuli. In most of the studies there was a significant negative correlation between age at disease onset and the movement outcomes, suggesting the impact of FRDA on the developmental unfolding of motor cognition.

A number of other studies have characterized impairment of cognitive function in FRDA. Fielding and colleagues examined antisaccade and memory-guided saccade characteristics in 13 individuals with FRDA and matched control participants (304). Individuals with FRDA demonstrated significant changes in the cognitive control of ocular movements compared to controls. Likewise, Hocking and colleagues (2010) employed a gap overlap task to examine attentional engagement and disengagement of eye movements in FRDA (252). People with FRDA were able to move attention promptly in the absence of a distracter however had difficulty disengaging attention to engage with a target in the presence of a distracter. In both studies, scores on a measure of clinical severity, the Friedreich Ataxia Rating Scale (FARS) significantly correlated with outcome measures (252, 304).

Klopper and colleagues examined sustained volitional attention and working memory in a cohort of 16 individuals with FRDA and matched control participants (305). Individuals with FRDA demonstrated significant impairment in attention and working memory providing evidence for a disruption to the network of brain regions that modulate and underlie working memory and attentional capacity.

More recently Nieto and colleagues examined performance on a tasks measuring information processing speed, attention, executive function, working/visual and verbal memory, visuoperceptive/visuospatial and visuoconstructive function and language in 36 people with FRDA compared to matched control participants (306). People with FRDA demonstrated impairment in all domains when compared to controls. As with previous studies Nieto and colleagues concluded such impairment was a result of disruption to cerebro-cerebellar circuits critical to cognitive function.

2.14.3 Scientific basis on which the guidelines were developed

Results from these empirical studies suggest the presence of cognitive impairment in people with FRDA however the degree to which this is apparent varies (Level lll -2 evidence). One of the following explanations may account for such impairment in people with FRDA: 1) cortical pathology, 2) dysfunction in the cerebellum interrupting cerebro-ponto-cerebellar-thalamo-cerebral loops, or 3) a combination of the two. Impairment in cognitive function in people with FRDA may be indicative of disruption to the cortico-cerebellar neural network reflecting a failure to access prefrontal, frontal and parietal regions necessary for effective cognitive control (173, 281, 282, 300, 306-310, 311).

2.14.4 Future research directions

The most effective avenue to explore cognitive function is usually through the use of paradigms that report RT. Given the impact of FRDA on motor control, attempting to characterize cognitive function in FRDA using RT may lead to false positive results. Most of the reported studies have utilized RT to evaluate cognitive capacity. Individuals with FRDA have impairment in cognitive function likely as a consequence of disruption in the neural connectivity between the cerebellum and cortical structures usually implicated in complex cognitive functions. Further study utilizing non-motor techniques are required to confirm these findings.

Further research in this area will provide an opportunity to take the previous findings, particularly regarding the neurobehavioral profile of individuals with FRDA, and apply them to the development and evaluation of appropriate intervention that aims to improve functional capacity. Moreover, understanding the neurobehavioral profile associated with FRDA is fundamental to intervention aimed at improving independence, school, academic and vocational capacity and thus quality of life.

2.14.5 Recommendations

Recommendations	**Grade**
Consideration should be given to changes in cognitive function that may impact on independence.	GPP
The impact of cognitive capacity on academic skills should be considered in academic environments.	GPP

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2.15 Rehabilitation

Authors: Ms Sarah Milne, Ms Emma Campagna, Dr Louise Corben.

2.15.1 Overview

People with Friedreich ataxia (FRDA) may benefit from rehabilitation to counteract the effect of ataxia, weakness and spasticity on function (312). Reduction of muscle activity, and hence joint movement, can result in adaptive anatomical, mechanical and functional changes to the neural and musculoskeletal systems (313). These include loss of functional motor units, changes in muscle fibers and muscle metabolism, and increased muscle stiffness (314, 315). Lack of muscle activity can also lead to osteoporosis, muscle wasting and malalignment of joints from muscle imbalance (13, 316). In addition, generalized weakness and increased fatigue may be a consequence of disuse (315). As both residual muscle strength and motor activity are determinant factors of a high level of functional independence, secondary adaptations as well as the potential for neuroplasticity are both areas which rehabilitation should aim to impact (317-319).

Rehabilitation is likely to improve function through modification of secondary adaptations caused by de-conditioning, and may influence the effect of the non-neurologic symptoms such as cardiomyopathy (178, 320). FRDA produces secondary consequences such as muscle atrophy and associated loss of sarcomeres, tendon length and connective tissue elasticity (317). Rehabilitation may produce physiological changes to these processes including muscle fiber hypertrophy, increasing numbers of sarcomeres, an increase in tendon and connective tissue length and pain relief (225). In addition, education regarding disease progression, strategies for compensation and equipment prescription may improve functional independence in people with FRDA (14, 184, 199, 319).

2.15.2 Literature review regarding rehabilitation in Friedreich ataxia

A literature search revealed nine articles related to this topic. These articles dated from 1988 to 2012. Table 6 provides a brief overview of each article.

Setting of rehabilitation

Rehabilitation can be provided in specialized inpatient or outpatient rehabilitation facilities, and/or in the home, school or community environment. Multi-disciplinary rehabilitation, which includes a dedicated team of medical, nursing and allied health staff with specialist skills in rehabilitation of people with FRDA is the cornerstone of a coordinated rehabilitation program (177, 321). Allied health interventions may consist of physical therapy, occupational therapy, speech pathology, dietetics, orthotics,

psychology, social work and exercise physiology. In addition to multi-disciplinary rehabilitation, single discipline therapy can also be used to address elements of functional decline in maintaining independence (12, 184).

Indications for rehabilitation

Rehabilitation may be applicable to people with FRDA at varying ages and stages of the disease process and may be beneficial both proactively and reactively in delaying, maintaining and improving functional decline for the individual with FRDA (14, 184). In a study by Milne and colleagues (14), inpatient rehabilitation admissions were due to deterioration in function, risk of losing capacity to mobilize or transfer independently as well as following pharmacological management for lower limb spasticity. Intensive rehabilitation may also be indicated to maximize function following orthopedic surgery (6, 14), and may also be beneficial at critical times in the natural progression of the disease such as transition to gait-aid or wheelchair or following acute illness and bed rest (14, 184, 199).

Types of rehabilitation

Continuous (Maintenance) Rehabilitation

Individuals with FRDA may benefit from daily exercise to maintain their physical function and prevent any complications caused by de-conditioning. Ilg and colleagues reported maintenance of improvement in function achieved during inpatient rehabilitation was dependent on continuous ongoing training post-discharge (133). Continuous rehabilitation may comprise a home exercise, gym, hydrotherapy, standing and/or community based program. Continuous rehabilitation is particularly beneficial if the demands of usual daily activities are not sufficient to maintain or improve physical capabilities (317).

School Environment

Rehabilitation for younger people with FRDA may be beneficial when based in a school environment. Whilst there is no direct evidence for young people with FRDA, studies examining children with other disabilities such as cerebral palsy have demonstrated school based interventions are most effective for the integrated delivery of services to everyday home, school and community activities (322). For children with disabilities, some of the benefits of having rehabilitation in the school setting include therapists, teachers and parents working together to identify and design relevant interventions for the child. Compatibility between education and therapy service delivery is vital as both disciplines recognize the importance of providing cognitive, social, communication and motor learning activities. Equal participation, effective communication, joint decision-making about student educational goals, agreement about the type and quantity of

therapy support needed, infusion of knowledge and skills from different disciplines into the design of educational strategies, and joint problem-solving and shared responsibility for student progress are all critical in the process (323).

Short Term Intensive Rehabilitation

Intensive rehabilitation is beneficial in improving function for people with FRDA (14). Intensive rehabilitation is best provided in a short burst to provide stimulus to the neuromuscular system via demands for activation of control mechanisms for balance (133). Intensive rehabilitation has also been shown to improve the function of people with other neurodegenerative diseases such as multiple sclerosis, Huntington disease and Parkinson disease that require an integrated approach from a number of disciplines (324-326). Intensive rehabilitation may be provided in an inpatient, outpatient or community setting. The benefits of intensive rehabilitation appear to have some carry over into the community and may persist over time (14, 133, 326, 327).

The individual disciplines that contribute to the multidisciplinary approach include:

<u>Land based physical therapy</u>
Physical therapy treatment is based on a comprehensive assessment of function, sensory and motor impairments. Interventions by the physical therapist may include strengthening, facilitation of normal muscle activity, balance exercises in sitting and standing, functional retraining and education, home exercise program development, stretching utilizing manual and assistive devices such as standing machine or tilt table or serial casting. Key areas of physical therapy rehabilitation for people with FRDA are: maintaining and improving the alignment of body segments in relation to each other and the base of support; postural control; the changing interplay between closed- and open-chained movements affected by the increased use of the upper limbs and trunk in mobility; fixation and dynamic stability (328, 329) and providing appropriate strategies, techniques or equipment for improved function.

<u>Aquatic physical therapy</u>
Aquatic physical therapy may be a beneficial adjunct to land-based rehabilitation and is usually indicated to decrease muscle tone, improve postural stability and increase functional mobility (330-332). Due to the high incidence and heterogeneity of cardiac abnormalities in people with FRDA (333, 334) careful assessment of heart function is crucial before immersion in water. At immersion in 35ºC water to the sternal notch, individuals have increased central vascular engorgement and therefore a 34-50% increase in stroke volume and cardiac output (335). The heart of a person with FRDA is potentially affected by increased vascular engorgement and increased cardiac output. The subsequent vascular shift has the potential to overstrain the cardiovascular adaptive mechanisms and lead to cardiac decompensation (336). In the first instance the aquatic

physical therapist should consult the treating cardiologist to ascertain if this therapy is appropriate for the specific person with FRDA.

If considered appropriate, aquatic physical therapy can include standing balance, core stability training, muscle strengthening and stretching. The physical properties of water, including buoyancy, viscosity of water, turbulence, heat and hydrostatic pressure can create benefits from immersion, including ability to exercise without having to work against the force of gravity, ability to balance with decreased speed of balance reactions required to remain upright, ability to progress strengthening exercises gradually from a level lower than gravity grades 1-3 (Oxford scale), reduced manual handling for the therapist and increased flexibility of muscles (331, 337, 338).

Exercise Physiology

There is considerable evidence on health benefits of physical activity in the general population (339). It is reasonable to therefore assume that people with FRDA will also benefit from regular exercises. Negative adaptive changes to the cardiovascular system may arise from the lack of physical activity (315) and, although there is no evidence that physical activity would slow down the progress of the disease, improving and maintaining general strength and cardiovascular fitness may help people with FRDA in maintaining their independence at the optimal level. Regular physical activity on most of the days in a week including strengthening exercises twice a week is recommended. Due to cardiac impairment often associated with FRDA (333), individuals should undergo a comprehensive medical assessment before commencing any exercise program. Intensity of the exercise program should be kept at the moderate level and supervised by a qualified Exercise Physiologist (340).

Occupational Therapy

Occupational therapy provides a holistic assessment of an individual's functional abilities relating to their daily activities. Occupational therapy intervention for people with FRDA generally includes: assessment and exercise programs designed to improve upper limb function and prevent musculo-skeletal changes related to FRDA; prescription and provision of equipment to maximize independence and participation in daily activities; modifications to the home and/or work environment to maximize safety and facilitate independence; retraining of functional skills; assessment, prescription and training in the use of manual or motorized wheelchairs; assessment and management of pressure care issues; assessment and management of school, educational and vocational issues.

Speech Pathology

Speech pathology can be provided as a single discipline or as part of the multidisciplinary team. In incorporating the rehabilitation approach, the speech pathologist may work with the occupational therapist, nursing staff or dietician to ensure the intervention can be incorporated into the rehabilitation program and

ultimately function. The rehabilitation setting may provide a useful environment to practice the strategies provided by the speech pathologist. Please refer to sections 2.7 and 2.8 for further information regarding speech and swallowing.

2.15.4 Evidence related to benefits of rehabilitation

The goals of rehabilitation are to facilitate function, increase levels of independence and prevent secondary complications (318). Theoretically, the beneficial aspects of rehabilitation can be explained by the process of rehabilitation causing sufficient overload to produce a physiological response, which in turn enhances the ability to recruit motor units (317). During and after the rehabilitation process, function and strength can continue to improve which is directly attributable to morphological changes within the contractile tissue inducing muscle fiber hypertrophy (317). Whilst the exact mechanism underlying the benefits of rehabilitation in people with FRDA remains unclear, it is apparent that a period of inpatient rehabilitation may reverse or halt the downward decline in function seen in most people with FRDA. Moreover the benefits from rehabilitation may continue during the period immediately following inpatient rehabilitation demonstrating the importance of maintaining an ongoing regular program of exercise (14).

2.15.5. Future research directions

Due to the lack of effective disease modifying pharmacological treatment for FRDA, rehabilitation has been used to manage the negative effects of the disease on mobility and function (14). However there is minimal documented evidence on the benefit of rehabilitation for individuals with FRDA. In addition the evidence for other spinocerebellar degenerative diseases is also sparse (341). Further evaluation of the effect of rehabilitation is crucial in order to determine appropriate criteria for rehabilitation and should document intensity, type and length of rehabilitation to determine the most appropriate intervention to maximize function for individuals with FRDA.

2.15.6. Recommendations

Recommendations	Grade
Intensive inpatient rehabilitation is beneficial in improving function for people with FRDA.	C (14)
People with FRDA may require a cardiological opinion prior to undergoing aquatic physical therapy.	GPP
Rehabilitation may be provided in various home or community based settings.	GPP
Rehabilitation should be provided by allied health staff with expertise in neurological conditions.	GPP

People with FRDA may benefit from maintenance rehabilitation and regular review of function.	GPP

Table 6 Summary of literature related to rehabilitation in Friedreich ataxia

Authors/Year	Article	Study Type	Participants	Intervention	Outcome Measures	Conclusion
Blattner et al (11)	Friedreich's ataxia: a suggested physical therapy regimen.	Opinion	N/A	N/A	N/A	Physical therapy can assist the patient with FRDA improve quality of life through strengthening, stretching, functional retraining and coordination exercises.
Fillyaw et al (342)	Endurance exercise training in Friedreich ataxia.	Case study	N=1. A 38-year-old man with FRDA	27 exercise sessions on the bike ergometer, 20 to 25 minutes each session, achieving an exercising heart rate equal to 70% to 85% of pretest maximum, and pre and post stretching routines.	Peak VO2, peak ventilation, work capacity.	A medically supervised endurance training program can increase aerobic work capacity and promote weight loss in patients with FRDA.
Harris-Love et al (197)	Rehabilitation management of Friedreich ataxia: lower force extremity force-control variability and gait performance.	Case Study	N=1. 14 y.o. with FRDA, mobility with rolling walker and wheelchair.	12 month period of two sessions per week of physical therapy for task orientated reaching activities, muscle stretching, functional strengthening, therapeutic exercise for hip and trunk musculature and gait training with U-Step Walking Stabilizer (USWS).	Nine-hole peg test, single leg stance time, manual muscle testing, gait parameters.	Progressive decline in gait parameters. USWS appeared beneficial in reducing falls.
Delatycki et al (6)	Surgery for equinovarus deformity in Friedreich's ataxia improves mobility and independence.	Prospective cohort	N=36 (n=9 for surgery), homozygous for a GAA expansion. Exclusion criteria end stages of the disease .	Lengthening of Achilles tendon to correct equinus deformity.	MBI, FIM, FIM mobility subscale, five-item Barthel.	Surgical intervention can improve mobility and standing transfers.
Goulipian et	Orthopaedic shoes	Case Study	N=1. 26 y.o female	Orthopedic shoes for one	Clinical gait assessment.	Improvement in quality

al (198)	improve gait in Friedreich ataxia: a clinical and quantified study.		with FRDA. Able to ambulate with a stick. Pes cavus and clawed toes.	month.	Quantified gait assessment. Self-assessment.	of life as reported by the participant. Increased speed of gait, step length and cadence.
Ilg et al (133)	Intensive co-ordination training improves motor performance in degenerative cerebellar disease.	Intra-individual control design, prospective cohort study	N=16 (FRDA n= 3). Degenerative cerebellar disease. Inclusion criteria: able to ambulate with or without an aid.	Four weeks, 1 hour sessions, 3 times per week. Static balance, dynamic balance, whole body movement and treatment of contracture if applicable.	SARA, ICARS, GAS, VICON, BERG balance test, gait measures.	Improvement in multi-joint co-ordination and dynamic balance with intensive training. Maintenance of improvement if a home exercise program is performed by the participant.
Ciancarelli et al (297)	Evaluation of neuropsychological functions in patients with Friedreich ataxia before and after cognitive therapy.	Prospective Cohort Study	N=24. People with FRDA attending inpatient rehabilitation.	Cognitive rehabilitation therapy (sequential treatments) performed during a scheduled study period during three separate periods of inpatient rehabilitation over one year.	MMSE, the Rey 15-item Memorization Test, Raven's Colored Progressive Matrices, Phonemic Verbal Fluency Test, Symbol Digit Modalities Test, Zung scale, Stroop color-word interference task.	One-year cognitive rehabilitation therapy may contribute to reducing cognitive decline.
Ciancarelli et al (343)	Disability and occupational therapy in patients with Friedreich's ataxia.	Prospective Cohort Study	N=10. People with FRDA attending inpatient rehabilitation	Occupational therapy during three separate inpatient rehabilitation periods over one year.	Barthel Index, Katz Index, 9 Hole-Peg Test, Klockgether Scale.	Functional independence improved and neurological deficits in the upper limb remained stable over a one year period after occupational therapy intervention.
Milne et al (14)	Retrospective study of the effects of inpatient rehabilitation on improving and maintaining functional independence in people	Retrospective Cohort Study	N=29. People with FRDA admitted to inpatient rehabilitation from 2003-2010.	Multidisciplinary inpatient rehabilitation for a variable time with length based on the patients' goals.	FIM	Function improved after rehabilitation and was maintained or continued to improve for the immediate time period following.

	with FRDA .					

Legend

SARA – Scale of the assessment and rating of ataxia
ICARS – International cooperative ataxia rating scale
VICON- Vicon motion measurement system
BERG – Berg balance test
MBI- Modified Barthel Index
FIM – Functional Independence Measure
USWS - U-Step Walking Stabilizer

3. The Heart, Cardiovascular and Respiratory System in Friedreich ataxia

3.1 The Heart

Authors: Dr Roger E Peverill, Professor David Lynch, Dr R. Mark Payne**.**

3.1.1 Overview

FRDA is commonly accompanied by abnormalities of both cardiac structure and function, and cardiac disease is the main cause of death in this condition (81). Individuals with FRDA can experience arrhythmias, most commonly of atrial origin, and symptoms due to arrhythmias can include palpitations, dizziness, dyspnea and chest discomfort. Individuals with FRDA can also develop heart failure with its associated symptoms, and the combination of heart failure and arrhythmia conveys a poor prognosis (81). Deficiency of the protein frataxin is the fundamental abnormality which leads to expression of the cardiac phenotype of FRDA (344). As a result of the mutations in both alleles of the *FXN* gene and the decreased frataxin there is impaired assembly of iron – sulphur clusters that are critical to key enzyme functions in mitochondria and throughout the cell

There has been no consistent definition or terminology used in the published studies to describe the features of the cardiac involvement in FRDA (59, 71, 345-350) and this lack of consistency has made interpretation of, and comparison between, studies difficult. The most common description of the cardiac phenotype in FRDA has been "hypertrophic cardiomyopathy", yet there are reasons to question whether this is the best terminology in FRDA. One important concern is that using the term hypertrophic cardiomyopathy in FRDA leads to confusion with the autosomal dominant conditions that are also termed hypertrophic cardiomyopathies. This is an important distinction as there are fundamental molecular and clinical differences between FRDA and these autosomal dominant conditions which have implications for both outcomes and treatment. First, the mechanism which underlies the cardiac changes in FRDA is based on frataxin deficiency in the mitochondria, whereas in the autosomal dominant hypertrophic cardiomyopathies it is sarcomere abnormalities and myocardial fibre disarray (351). Second, the pattern of hypertrophy in FRDA is generally concentric, uncommonly asymmetric and there is rarely any outflow tract obstruction; this is unlike the pattern seen in the autosomal dominant hypertrophic cardiomyopathies, which most frequently is asymmetric septal hypertrophy, often in association with a resting or inducible outflow tract gradient (352) Furthermore, while the term hypertrophic also implies an increase in left ventricular mass index (LVMI), a common pattern of LV remodelling in

FRDA is an increase in relative wall thickness (RWT) in the absence of an increase in LVMI (333, 353). Even in the absence of any definite increase in RWT or LVMI, abnormalities on the electrocardiogram can occur (EKG; (79), suggesting that there is at least some degree of myocardial abnormality in the majority of FRDA individuals. Individuals with FRDA can also have a dilated left ventricle with reduced LV ejection fraction (LVEF), i.e. a phenotype consistent with a dilated cardiomyopathy. LV dilatation and reduced LVEF are generally not seen in FRDA at first presentation, indicating that there can be evolution to this cardiac phenotype later in the disease process. On the basis of the issues discussed above, the heterogeneous and unique collection of cardiac abnormalities seen in FRDA might be better described as the "FRDA cardiomyopathy".

Isolation of the effects of frataxin deficiency on the heart in FRDA requires awareness of the possibility of cardiac effects from coexistent conditions. Diabetes mellitus occurs in approximately 10% of individuals with FRDA (58, 67) and is known to have effects on cardiac structure and function (354). Sleep apnoea is also recognized to have effects on the heart (355-357), is more common in FRDA than in the non-FRDA population and has been reported to occur in young adults with FRDA even in the absence of morbid obesity (34). Hypertension and ischemic heart disease would be predicted to become more common with age in FRDA, as they do in the non-FRDA population. Hypertension can lead to, and in FRDA presumably contribute to, similar changes in cardiac remodelling (concentric remodelling and concentric hypertrophy) as can be seen early in the course of FRDA in the absence of hypertension (358). On the other hand, ischaemic heart disease can lead to regional and possibly global hypokinesis of the left ventricle and these abnormalities can also occur late in the disease course in FRDA. Other acquired heart disease in the FRDA population is not common but should also be kept in mind. For example, myocarditis is not a common condition but can occur at any age and because of the underlying cardiac abnormality, individuals with FRDA could be more susceptible to its effects. Furthermore, cocaine use (359) and alcohol abuse (360) are both recognized to have adverse cardiac effects.

The literature in FRDA can be loosely divided into studies before and after 1996, the year when the mutation in the *FXN* gene was first described. Most but not all studies published after 1996 have included subjects with genetic confirmation of the diagnosis of FRDA. The early studies still provide useful information about the cardiac phenotype in FRDA, but due to the lack of genetic confirmation it is very likely that these studies also included some subjects without FRDA (78, 361). Furthermore, individuals who were homozygous for GAA expansions in the *FXN* gene but with atypical neurological presentations would not have been included in studies prior to 1996 (60, 69). In addition, point mutations in the *FXN* gene are now recognized to occur in >2% of people with FRDA (101, 102, 362) and it likely that some of the subjects in the early studies will have had such point mutations. It is possible that there could be systematic differences

in the cardiac phenotype of individuals with FRDA due to a point mutation compared to homozygotes for GAA expansions.

3.1.2 Literature review of the structural and functional cardiac effects of Friedreich ataxia

Cardiac involvement in FRDA has been assessed by a number of non-invasive techniques, including electrocardiography (EKG), echocardiography and cardiac magnetic resonance (CMR; the last also accompanied on occasion by gadolinium enhancement, perfusion imaging and spectroscopy). There is only a limited amount of data regarding the natural history of cardiac disease in FRDA, particularly in the period since 1996 when genetic confirmation of the diagnosis became possible. There is limited pathological and histological data from post mortems and almost no cardiac biopsy data or catheterization-based data from living people with FRDA.

3.1.2.1 EKG

Most individuals with FRDA have evidence of cardiac involvement as determined by the presence of an abnormal EKG (68, 79, 82, 345, 361, 363). A recent study of 239 children and adults, 79% of whom had genetically confirmed FRDA, found EKG abnormalities in 90%, with the most common findings being nonspecific ST-T wave changes (53%), right axis deviation (32%), left ventricular hypertrophy (19%), and right ventricular hypertrophy (79). Females and those with shorter GAA1 repeats were less likely to have EKG abnormalities. Longitudinal follow-up data is still required to determine whether an EKG can assist in early diagnosis of FRDA-associated cardiomyopathy, aid in the assessment of prognosis, or help to define the underlying pathophysiological processes.

3.1.2.2 Echocardiography and cardiac magnetic resonance imaging

While the classical description of the cardiac disease of FRDA has been of a hypertrophic cardiomyopathy (59, 344), the nature and pattern of the LV structural change in FRDA is more complex than this and improving our understanding of FRDA cardiac disease will likely require more detail and precision in the terminology used. Structural abnormalities which have been frequently described in echocardiographic studies in FRDA are increase in left ventricular wall thickness (71, 333, 334, 348, 353, 364) and increase in left ventricular mass index (LVMI) (333, 348, 353, 364, 365). However, the most common abnormality in FRDA is an increase in RWT, with only a proportion of subjects with increased RWT also having an increase in LVMI (333, 353, 366). RWT is a convenient measure for the assessment of LV structural change in FRDA as, in distinction to LVMI, it is minimally affected by sex (367), although different thresholds in adults and children may be appropriate for the diagnosis of an abnormal RWT (367). While an increase in RWT without accompanying increase in LVMI (concentric

remodelling pattern) could just be an earlier stage of the hypertrophic process than a combined increase in RWT and LVMI (concentric hypertrophy pattern), there are alternative explanations for the relative lack of increase in LVMI in FRDA. An important component of the relative lack of increase in LVMI compared to RWT in FRDA is that the LV remodelling in FRDA is not just reflected in an increase in wall thickness but also by a decrease in LV end-diastolic cavity size (333, 334, 365), the latter change necessarily associated with a lower LVMI than if the cavity size had not decreased. Another important observation from several cross-sectional studies in adults is that LVMI is inversely correlated with age (364, 365, 368) and therefore additional possible explanations for the relative lack of LVMI increases in FRDA could be ageing-related LV remodelling, premature mortality or morbidity in individuals with FRDA with higher LVMI or a combination of both processes.

An additional accompaniment of the reduced LV end-diastolic volume in FRDA, in the absence of an increase in, rather than just preservation of LVEF, must be a reduction in stroke volume (365, 366). This would be predicted to lead to a decrease the cardiac output even in the face of preserved LVEF. However, the cardiac output is at least partly preserved in FRDA despite the lower stroke volume due to a higher heart rate compared to control subjects (333, 366).

There is only limited data on the effects of FRDA on Doppler measures of left ventricular relaxation and filling, including transmitral E and A, their ratio (E/A) and isovolumic relaxation time (IVRT), in comparison with age- and sex-matched control subjects. Furthermore, the results have not been consistent (333, 334, 346, 366, 369). One issue not always considered in previous studies is that A is positively correlated with heart rate and therefore the E/A ratio is inversely correlated with heart rate (370). The higher heart rate in individuals with FRDA should have been, but was generally not, adjusted for in comparisons with control subjects.

While LVEF is generally preserved in FRDA, other markers of LV systolic function are reduced. Both systolic and early diastolic myocardial velocity gradients of left ventricular short axis function (reflecting radial systolic and early diastolic strain) were reduced compared to control subjects in a group of individuals with FRDA who were free of cardiac symptoms (334). Tissue Doppler measurements of longitudinal function in FRDA subjects with preserved LVEF showed reduced peak velocities of both systolic and early diastolic left ventricular motion as well as of atrial contraction (333). Global longitudinal strain and peak systolic twist are also reduced in individuals with FRDA with normal LVEF and LVMI but increased RWT (366). Whether there is clinical or prognostic value of any of these measurements in FRDA is unknown at this time.

Left atrial dilatation is a sign of chronic elevation of left atrial pressure(371) and left atrial size is thus of considerable interest in FRDA as it might be expected to increase in the setting of a small thick left ventricle. However, while there is limited information

about left atrial size in FRDA, available data suggests that it is not increased in individuals with increased RWT and normal ejection fraction (333, 366) In turn, this raises the possibility that the ratio of E/e`, which is elevated in FRDA (333, 366), and increases with LA pressure in other cardiac conditions (371), may not be an accurate reflection of left atrial pressure in FRDA.

A number of studies have reported relationships of GAA1 with LV structural changes in FRDA, but the findings have not been consistent. GAA1 has been noted to be higher in people with a "cardiomyopathy" (59, 80) and other reports include positive correlations of GAA1 with wall thickness (78, 372, 373), RWT (349), LV mass (78, 365), LVMI (71, 372) and an inverse correlation of GAA1 with LV end-diastolic dimension (368). On the other hand, there have also been recent moderate sized studies which have not replicated previous findings (348, 353). Potential explanations for these differences in results between studies include differences in the cohort characteristics and the limited size of individual cohorts. There has also been heterogeneity between the studies in the method of analyses, e.g. whether adjustments were made for potential confounding factors such as sex, age or body size. Neither is it clear that an adjustment for age is possible when children and adults are included together in these studies due to the complex nature of the differences between children and adults. First, heart rate is higher in children than adults and in children heart rate has a non-linear negative relationship to body size (374). Second, there is no sex difference in LVMI in children under 12 years but a higher LVMI in males becomes evident after age 12 and continues into and throughout adulthood (375). Third, the best method for indexing LV structures may not be BSA and may not be the same in children and adults (374). Fourth, RWT does not differ between the sexes but it does increase with age and therefore different RWT thresholds for the diagnosis of abnormality have been recommended depending on age (de Simone, 2005). Lastly, and of particular importance is that any FRDA cohort will necessarily be missing those individuals who have died prematurely from heart disease. As mortality is more likely to affect adults than children with FRDA (81), and occurs earliest in those with the most severe cardiac involvement (81), absence of individuals due to early mortality will likely confound any analysis which includes adults and children together.

GAA1 has not generally been correlated with LVEF or LV fractional shortening but has been reported to be inversely correlated with both systolic and early diastolic radial strain (334).

At least one polymorphism in a gene related to the renin-angiotensin system may also contribute to the cardiac phenotype of FRDA independent of GAA1 (368). The C allele of the *AGTR1* polymorphism rs5186 was not only more frequent in FRDA subjects than in a control population, but the C allele was also associated with greater septal wall thickness and LV mass in FRDA, independent of sex and body size. This suggests that the FRDA phenotype may be an interaction between *FXN* and other genes.

Using CMR spectroscopy, the cardiac phosphocreatine to ATP ratio was lower in individuals with FRDA with and without hypertrophy, implying that cardiac metabolic dysfunction in FRDA precedes hypertrophy and that it may play a role in the development of hypertrophy (376, 377). Using late gadolinium enhancement, myocardial fibrosis was identified in 58% of a cohort of individuals with FRDA with increased relative wall thickness but preserved LVEF (349). In the same study cohort, myocardial perfusion reserve index quantification revealed significantly lower endocardial-to-epicardial perfusion reserve in subjects with FRDA versus controls, whereas there was no difference in myocardial iron between the two groups using the CMR technique of T2*. The former finding suggests a greater potential for subendocardial ischemia in FRDA in situations where cardiac perfusion reserve is under stress (e.g. atrial fibrillation with a rapid ventricular response). The latter finding implies that the intra-mitochondrial iron particles in FRDA are relatively isolated compared with the large iron aggregates seen in transfusion-associated myocardial iron overload making CMR measurement of iron content in the FRDA heart uninformative for guiding therapeutic interventions.

3.1.2.3 Natural history studies

There are limited prospective and no long-term natural history studies of the cardiac manifestations of FRDA. There are a limited number of small medium-term studies, most performed before the identification of the *FXN* gene.

There is limited data with regard to LV remodeling with time in FRDA and most is from the time before genetic confirmation was possible. Nevertheless, it is clear that the FRDA heart can remodel over time, although the predictors of such remodeling are unknown. In a five year follow-up of 10 individuals with FRDA, the three people who initially had the smallest indexed left ventricular diastolic dimensions developed dilatation of their left ventricles and atria, with an accompanying decrease in LV contraction and either stable or decreasing LV wall thickness (378). In contrast, the other seven individuals with initial indexed LV diastolic dimensions closer to normal did not develop significant dilatation. There was, however, a gradual increase in LV wall thickness in this subgroup. In a 5-year echocardiographic follow-up of 61 subjects with FRDA, increased LV wall thickness was evident at the initial echocardiogram in 75% of cases and remained unchanged throughout the entire follow-up period. In one case left ventricular hypertrophy evolved into a dilated cardiomyopathy (379). In a further follow-up study from the same group, over 8 years 17% of 66 subjects with FRDA developed a dilated hypokinetic left ventricle. Most of those who developed LV dilatation and hypokinesis were said to have a hypertrophic left ventricle at baseline, although the definition of LVH used in this study was non-standard (380). In a median 5 year prospective echocardiographic follow-up of subjects with FRDA most of whom (61/70) were taking idebenone, there were decreases in posterior wall thickness, LVMI

and ejection fraction (71). The combination of decrease in LVMI and ejection fraction is unlikely to reflect cardiac improvement.

In a retrospective analysis of LV structural and functional changes during follow-up in 23 subjects with FRDA there was a slow nonlinear decline in systolic function over time, with the mean LVEF decreasing more rapidly as age increased but there was maintenance of LVEF in the normal range until the age of 22 years (381). Of the 12 subjects with systolic dysfunction and follow-up echocardiograms, 10 showed improvement to the normal LVEF range on at least one echocardiogram, and 5 remained normal through the last study. However, this cannot be concluded to reflect spontaneous improvement as LVEF is dependent on and therefore will vary with loading conditions, while echocardiographic assessment of LVEF has an intrinsic variability (382).

Regression of LVH is recognized to have a beneficial effect on cardiovascular outcomes in hypertensive heart disease independent of blood pressure lowering (383) and it has been presumed by some that regression of LVH in FRDA must also be beneficial (51). However, it cannot be concluded that a reduction in LV wall thickness in FRDA is necessarily good in the absence of data that it leads to better clinical outcomes, or at the very least, of evidence that reduction in wall thickness is associated with an improvement in LV function. In contrast to hypertensive heart disease, increased LV wall thickness is not due to increased LV afterload in FRDA. Autopsy studies have shown that the LV wall becomes heavily fibrosed in later stages of FRDA cardiac disease and any increase in interstitial fibrous tissue is likely to be maladaptive. Furthermore, an important implication of the studies showing that the natural history of the LV involvement in FRDA can include an increase in LV size and a decrease in wall thickness is that in interventional studies in FRDA a decrease in LV wall thickness in an individual could actually represent spontaneous deterioration of the left ventricle. The complex and unpredictable nature of the components of LVH and their regression has been demonstrated in a study in which serial LV biopsies were performed before and after aortic valve replacement for aortic stenosis (384). Differences were evident in the time course of changes in LV mass, myocyte size and interstitial fibrosis and although there was an early reduction in LV mass, this was due to a decrease in myocyte size while there was actually a simultaneous increase in interstitial fibrosis (384).

3.1.2.4 Mortality studies

A study of 82 fatal cases of FRDA showed that over half the individuals died of heart failure while nearly three-quarters had evidence of cardiac dysfunction during life (82). In a population-based study of survival in FRDA in northwestern Italy, 58 individuals were identified and followed to death or to December 31, 1984 (whichever came first) to determine the patterns of survival (385). The 10-, 20-, and 30-year survival rates were 96%, 80%, and 61%, respectively. Survival for males was poorer than for females even after adjustment for expected survival. Somewhat unexpectedly, age of onset was not a significant prognostic factor.

In a follow-up of 61 individuals with FRDA cardiac failure was evident in 5% of the patients, and was the most common cause of death (379).

A retrospective study of subjects with FRDA was performed to determine cause of death followed by a case-control analysis comparing characteristics of deceased patients with living, age- and sex-matched FRDA controls (81). Causes of death were cardiac dysfunction (59%), probable cardiac dysfunction (3.3%), non-cardiac (27.9%) or unknown (9.8%). Compared to non-cardiac deaths, cardiac deaths occurred earlier in the disease course (median 29 vs. 17 years). Congestive heart failure and arrhythmia were common causes of cardiac-related death. Compared to living matched FRDA controls, deceased patients had longer GAA repeat lengths and higher rates of arrhythmia and dilated cardiomyopathy. The presence of "hypertrophic cardiomyopathy" did not differ between deceased and living patients.

3.1.2.5 Post mortem and biopsy studies

There are a number of post mortem studies in FRDA only two of which postdated genetic confirmation techniques (345, 386-389). In a post mortem study of 16 hearts from subjects with FRDA, including three complete hearts (386), all hearts showed extensive interstitial fibrosis with considerable focal degeneration of muscle fibres. One heart showed extensive active muscle necrosis. Antemortem cardiac thrombus and thromboembolism were common findings. The main coronary arteries showed no gross disease.

In a clinical study of 75 individuals with FRDA in which two died, post mortem revealed a minimally dilated but flabby left ventricle in both (345). Post mortem cardiac findings from 3 individuals with FRDA who died of congestive heart failure and atrial arrhythmias showed pleomorphic nuclei and focal fibrosis and degeneration throughout each heart, including in the conduction system (387). There were distinctive abnormalities of both large and small coronary arteries, and focal degeneration of nerves and ganglia.

In 18 post mortem specimens of individuals with genetically confirmed FRDA, histological sections revealed abnormal cardiomyocytes, muscle fiber necrosis, reactive inflammation, and increased endomysial connective tissue (388). Scattered muscle fibers displayed perinuclear collections of minute iron-positive granules in rows between myofibrils, but total iron in the left ventricular wall of individuals with FRDA was not significantly higher than normal. In a further study from the same group, regions of significantly increased iron were irregularly distributed throughout the working myocardium ((390). These observations are at odds with the concept of selective iron toxicity only in cardiac mitochondria, and the role of iron in mediating the cardiomyopathy of FRDA remains unknown.

There is minimal data available from cardiac biopsy in FRDA (388) and thus little information about the cardiac histology in individuals with early stages of the cardiac disease process. Based on post mortem data from individuals with more advanced cardiac disease, it might be assumed that there is a combination of myocyte loss, myocyte hypertrophy and interstitial fibrosis in the left ventricular wall of an individual with FRDA and increased RWT or LVMI. However, the age at which these individual components develop, whether they occur simultaneously or in some sequence and the temporal progression of these changes is unknown.

3.1.2.6 Late onset Friedreich ataxia

Late onset FRDA, defined as the onset of neurologic symptoms after age 25, is generally found in people with very short GAA1 repeat lengths, and may not be, or at least is less likely to be, associated with cardiac abnormalities (88, 144, 347, 391). Whether this means that cardiac screening is not necessary in late onset FRDA is not yet clear as there are only a small number of cases described in the literature. Until greater natural history data has accumulated, a conservative recommendation is to perform cardiac screening in all individuals with a diagnosis of FRDA.

3.1.3 Arrhythmias

3.1.3.1 Supraventricular arrhythmias in Friedreich ataxia

3.1.3.1.1 Literature review of supraventricular arrhythmias in Friedreich ataxia

Arrhythmias occur in FRDA, particularly in the later stages of cardiac disease, and cause morbidity and are also likely to contribute to mortality (81, 82). Intermittent palpitations have also been described in FRDA and the cause of these has not always been determined (68). Atrial fibrillation is the most common reported arrhythmia and may be paroxysmal or persistent (71, 82), but atrial flutter (68, 392) and atrial tachycardia have also been described. The combination of palpitations and angina has been reported in young people with FRDA (82), and it would not be surprising if individuals with a thick walled left ventricle and a strain pattern on the resting EKG could develop angina due to subendocardial ischemia in the setting of a tachycardia even in the absence of epicardial coronary artery disease.

Tsou and colleagues reported that arrhythmias were present or associated in ~16% of the deaths in FRDA (81). Although arrhythmia was listed either as the cause of death, or at least of playing a significant role in the death, there was insufficient detail from the records to determine the type of arrhythmia. Thus, the nature of the relationship of arrhythmia with mortality in FRDA remains unclear.

3.1.3.1.2 Rate controlling agents in atrial arrhythmias in Friedreich ataxia

No randomized controlled trial (RCT) has evaluated rate control of AF in FRDA but there are no specific reasons why standard guidelines for rate control should not apply in FRDA. Recommendations for heart rate control in atrial fibrillation are provided in the 2011 ACCF/AHA/HRS Focused Updates Incorporated Into the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation (33). In the initial management of a rapid atrial arrhythmia rate control with an AV node blocking agent is first line therapy in most circumstances. If there is heart failure or a possibility of reduced left ventricular ejection fraction then digoxin or amiodarone can be used safely, either intravenously or orally, although both require gradual loading and neither have a rapid onset of action as beta blockers. Furthermore, digoxin may have minimal effects at the onset of atrial fibrillation as it does not have any blocking action on the overactive sympathetic drive present at that time. In the absence of heart failure (HF) and reduced LVEF then a beta blocker is the most effective agent for rate control at the time of acute presentation. A calcium channel blocker (verapamil or diltiazem) is an alternative for rate control if beta blockade is contraindicated and there is no HF or reduction in LVEF. Either a beta blocker or calcium channel blocker can subsequently be combined with digoxin for additional AV node blocking effect if needed.

In general, rate control is not the preferred option for long-term management in atrial arrhythmias in FRDA as attaining and maintaining rate control, particularly during exercise in young people, can be very difficult. Furthermore, young people tend to remain symptomatic when in AF even if reasonable rate control can be achieved. Nevertheless, in certain circumstances, rate control may still be a reasonable option. In such cases digoxin can be used irrespective of the left ventricular ejection fraction. A beta blocker will be the preferred option if there is a history of heart failure or reduced ejection fraction, but needs to be commenced slowly. If there is reduced LVEF, verapamil and diltiazem are contraindicated because of their negative inotropic action.

3.1.3.1.3 Antiarrhythmic therapy for supraventricular arrhythmias in Friedreich ataxia

There are no RCTs which have examined the effectiveness or safety of antiarrhythmic drugs in FRDA for either reversion of atrial arrhythmias or for maintenance of sinus rhythm following spontaneous, chemical or electrical cardioversion. However, the 2011 ACCF/AHA/HRS Focused Update Incorporated Into the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation (33) can be used as a guide to antiarrhythmic treatment of AF in FRDA. There are important concerns raised in these guidelines about the safety of some of the antiarrhythmic medications in the setting of “organic heart disease” and it should be assumed that similar concerns apply to the abnormal heart in FRDA.

Of agents with proven efficacy for cardioversion of atrial fibrillation, flecainide, ibutilide and propafenone are not recommended in the setting of HF or organic heart disease

(33). This leaves amiodarone as the only agent with proven efficacy for cardioversion that can be considered as at least relatively safe for short term use in FRDA. Of agents with proven efficacy for maintenance of sinus rhythm, disopyramide, flecainide and propafenone are not recommended in HF or organic heart disease because of the potential for negative inotropic and proarrhythmic effects. Sotalol also needs to be used cautiously in HF and can have proarrhythmic effects, particularly in the setting of bradycardia. However, sotalol is not absolutely contraindicated in organic heart disease in the absence of HF or a reduced LVEF. This leaves amiodarone as an agent with efficacy for maintaining sinus rhythm which can be considered at least relatively safe for the heart in FRDA whether or not there is a reduction in LVEF. On the other hand, amiodarone has a number of other side effects, including hypothyroidism, hyperthyroidism, skin sensitivity and it can result in life-threatening pulmonary fibrosis.

3.1.3.1.4 Antithrombotic therapy for prevention of thromboembolism related to atrial arrhythmias in Friedreich ataxia

Based on data in subjects with AF and a dilated cardiomyopathy due to causes other than FRDA (33), a high risk for thromboembolism would be predicted for individuals with FRDA with AF and a reduced LVEF. Indeed, intracardiac thrombosis and systemic thromboembolism was described as a frequent finding in one post mortem study in FRDA (386). In the absence of any reduction in LVEF there are no specific reasons why the standard risk factors for thromboembolic risk in AF should not also apply to FRDA and therefore use of the $CHADS_2$ risk score (Table 8) may be a reasonable way to determine the need for anticoagulant therapy in FRDA. While an age >70 years will rarely apply in FRDA, diabetes is an important component of the $CHADS_2$ risk score and is more common in FRDA subjects than others in the community (33). Anticoagulation with a vitamin K antagonist is recommended for individuals with paroxysmal or permanent AF and more than one risk factor unless there is a contraindication (33). A number of new oral anticoagulants, including dabigatran, rivoroxaban and apixaban, have emerged as alternatives for vitamin K antagonists (VKAs) for thromboembolic prevention in patients with non-valvular AF (393). However, these new agents are not currently approved for use in children.

3.1.3.1.5 Ablation therapy in supraventricular arrhythmias in Friedreich ataxia

If the symptoms or ventricular response of supraventricular arrhythmias are unable to be controlled with antiarrhythmic and/or ventricular rate control medications then there is an option for AV node ablation or modification in combination with pacemaker insertion to prevent both a rapid ventricular response and bradycardia (33). Atrial flutter may be suitable for ablation therapy to prevent further episodes of atrial flutter. Atrial fibrillation can be treated with surgical or percutaneous procedures which include

pulmonary vein isolation but whether the pulmonary veins are a common site of origin of atrial fibrillation in FRDA is currently unknown.

3.1.3.2 Ventricular arrhythmias

3.1.3.2.1 Literature review of ventricular arrhythmias and sudden death in Friedreich ataxia

Ventricular tachycardia and fibrillation have rarely been described in FRDA and there are few reports of sudden unexpected death or syncope due to arrhythmia. Current evidence suggests that such events are not likely to be common in FRDA cardiomyopathy, particularly in the absence of LV dilatation and a reduction in ejection fraction. On the other hand, it cannot yet be concluded that these arrhythmias occur rarely in FRDA as natural history studies are lacking and furthermore, a single episode of either type of ventricular arrhythmia could result in sudden death in FRDA and yet not be documented. There is a single case of syncope due to a ventricular arrhythmia in an individual with FRDA which was managed with the insertion of an AICD (394). Two cases of sudden, unexpected death have been reported, one in a 4 year old boy with FRDA and a possible diagnosis of viral myocarditis, and the other in a 67 year old man with FRDA (389, 395). Further detailed data is required about the nature and frequency of ventricular arrhythmias in FRDA and there should be a low threshold for investigation with Holter monitoring and/or Loop monitoring in individuals with FRDA

3.1.3.2.2 Antiarrhythmic therapy for ventricular arrhythmias in Friedreich ataxia.

There are no RCTs which have addressed the effectiveness or safety of antiarrhythmic drugs in FRDA for the treatment of ventricular arrhythmias. Furthermore, as there are few reports of symptomatic ventricular tachycardia, syncope due to ventricular tachycardia or resuscitated sudden death in FRDA, antiarrhythmic therapy to prevent recurrent ventricular arrhythmias will rarely be indicated. With the exception of beta blockers, no currently available antiarrhythmic drugs have been shown in RCTs to be effective in the primary management of patients with life-threatening ventricular arrhythmias or in the prevention of sudden cardiac death (SCD) (396). On the other hand, beta blockers are effective in suppressing ventricular ectopic beats and arrhythmias as well as in reducing SCD in a spectrum of cardiac disorders in patients with and without HF (396). As a general rule, antiarrhythmic agents may be effective as adjunctive therapy in the management of arrhythmia-prone patients under special circumstances. Because of potential adverse side effects of the available antiarrhythmic drugs, these agents must be used with considerable caution.

If individuals with FRDA develop ventricular arrhythmias, then beta blockers should be considered first-line therapy for secondary prevention, but if not effective at full therapeutic doses, then amiodarone or sotalol can be tried, with careful monitoring for

adverse effects during administration. Amiodarone is the only option if beta blockers are contraindicated. Both sotalol and amiodarone have also been shown to reduce the frequency of ICD shock therapy. Sotalol should be avoided in patients with HF, severely reduced LVEF or renal dysfunction.

3.1.3.2.3 ICD for primary and secondary prevention of ventricular arrhythmias in Friedreich ataxia

There is no RCT data regarding ICD implantation for either primary or secondary prevention of ventricular arrhythmias in FRDA. Multiple clinical trials in other cardiac conditions have demonstrated a survival benefit of ICD use compared to antiarrhythmic therapy for secondary prevention of resuscitated SCD, sustained ventricular tachycardia (VT) or sustained ventricular fibrillation (VF). It is recommended that the ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities be used to guide ICD placement for the secondary prevention of SCD or sustained VT/VF in FRDA (32). Importantly, these guidelines do not support ICD placement if the predicted lifespan from other causes is less than a year.

Primary prevention of SCD refers to the use of ICDs in individuals who are at risk for but have not yet had an episode of sustained VT, VF, or resuscitated cardiac arrest. Clinical trials have evaluated the risks and benefits of ICD implantation in prevention of sudden death and have shown improved survival with ICD in multiple patient populations, including those with HF due to non-ischemic dilated cardiomyopathy (32). However, making recommendations for primary prevention in FRDA is difficult due to the lack of natural history studies in FRDA.

For primary prevention, individuals with FRDA may fall into 3 categories where the ACC/AHA guidelines suggest that an ICD should be considered:

3.1.4.1 Dilated cardiomyopathy with LVEF <35% and NYHA class II or III. Implanting an ICD is recommended in such patients based on more than one RCT (32). However, it may be difficult to determine the NYHA functional class in individuals with advanced FRDA because the main cause of their functional limitation may be their neurological status. Importantly, development of a dilated cardiomyopathy may be more common than previously suspected in FRDA based on the study by Tsou et al, which showed these features present in 65% of FRDA death for which data was available (81) Thus, ICD implantation may be justified in some FRDA individuals with a dilated cardiomyopathy.

3.1.4.2 Increased left ventricular wall thickness with risk factors. However, current recommendations for ICD placement in the presence of hypertrophy are based on outcomes in the autosomal dominant hypertrophic cardiomyopathies (resulting from mutations in contractile proteins) where there is documentation of a significant rate of sudden death (397). Placement of an ICD as a preventative

strategy in the absence of significant risk factors may be harmful (Class IIIC).

3.1.4.3 Patients with an LVEF <35% who are in NYHA class I and have a non-ischemic cardiomyopathy. The guideline recommendations are to consider an ICD (Class IIb) but the evidence for benefit is not as strong as it is in symptomatic patients (32).

One series of five subjects with FRDA who received ICD implantation has been reported (ages from 14-26 years) (398) However, none of this cohort had syncope, near syncope, symptomatic ventricular tachycardia or a dilated cardiomyopathy with reduced LVEF (i.e. there were no standard indications for an ICD).

3.1.4 Heart Failure

3.1.4.1 Literature review of heart failure in Friedreich ataxia

The symptoms of HF may be recognized later in FRDA because dyspnoea and/or fatigue with exertion will be less prominent clinical features in an individual who is wheel chair bound. The spontaneous development of HF symptoms or signs in individuals with FRDA and normal ejection fraction is rare, even if there is severe increase in RWT or LVMI. The presence of HF symptoms and signs therefore suggest a reduced LVEF. HF from cardiomyopathy is the primary mode of death in ~60% of patients with FRDA. In a recent retrospective review, Tsou and colleagues identified a history of HF in approximately 65% of patients dying from FRDA (81).

3.1.4.2 Classification of heart failure in Friedreich ataxia

The American College of Cardiology (ACC) and American Heart Association (AHA) have developed a classification of HF based on stages of the syndrome (Table 8) and this classification can be used as a guide to treatment strategies (31). The classification is based on the assessment of the risk for developing HF. Stage A includes patients who are at risk for developing HF but who have no structural (remodeling) heart disease at present. The aim of the management strategy in this group is prevention of HF. A relevant example in FRDA would be a young person with a recent diagnosis of FRDA but who does not have evidence of cardiac involvement on history, examination or imaging. Stage B includes individuals with evidence of structural changes of the heart but no symptoms. The management goal is prevention of progression of the left ventricular remodeling and the development of HF. A relevant example would be an individual with FRDA who has increased LV RWT on echocardiography but does not have any significant limitation to daily activities or arrhythmias. Stage C includes people with structural heart disease with current or prior symptomatic HF. A relevant example would be an individual with FRDA who has a dilated hypokinetic left ventricle and HF symptoms. Stage D includes patients with severe refractory HF. Patients in this stage may be

considered for high-technology therapies such as heart transplantation or mechanical circulatory support but end-of-life care may be more appropriate in some cases.

The New York Heart Association (NYHA) HF classification scheme is used to assess the severity of functional limitations (ability to exercise) and there is a correlation of this classification with outcomes (Table 9) (399). However, the NYHA classification scheme has limitations for the assessment of individuals with neuromuscular disorders due to the inability of some such individuals to perform exercise. Therefore, the assessment of risk for developing HF (Table 10) will be a more widely applicable strategy for the classification of heart disease severity in FRDA. NYHA Stage I is when there are no symptoms related to the heart even during exercise, such as climbing two flights of stairs. This stage may be easy to determine in a person newly diagnosed with FRDA, but becomes more difficult to assess as the neurologic features of FRDA advance and lead to limitations of mobility. Stages II and III are difficult to assess in FRDA because loss of ability to exercise is common in advanced neurologic disease. Thus, it could be difficult to tell if HF is advancing using this classification. Stage IV is easier to assess as cardiac symptoms with rest or minimal activity and particularly orthopnea and paroxysmal nocturnal dyspnea are more specific for cardiac disease.

3.1.4.3 Pharmacologic treatment of heart disease in individuals with Friedreich ataxia with normal ventricular ejection fraction.

There is currently no evidence to support any cardiac treatment for individuals with FRDA with normal LV ejection fraction and without cardiac symptoms or signs. A number of studies have investigated the effects of idebenone on LV wall thickness and/or LV mass but most of these studies have been small and the findings have not been consistent (summarized by Lynch and colleagues (344)). Furthermore, a reduction of wall thickness or LV mass cannot be assumed to be a beneficial outcome of treatment in FRDA.

Spontaneous onset of HF symptoms is rarely if ever seen in FRDA subjects with increased LV wall thickness in the setting of a normal ejection fraction and so regular HF medication therapy is unlikely to be indicated in individuals with FRDA with a normal LVEF. However, individuals with FRDA with such patterns of LV remodeling are more likely to develop symptoms and signs of acute HF in circumstances of stress such as operations and serious infections, particularly if accompanied by marked changes in intravascular volume. Careful fluid management to avoid depletion or overload is recommended in such situations and diuretic therapy could be required if symptoms or signs develop due to fluid overload.

3.1.4.4 Pharmacologic treatment of heart failure with reduced left ventricular ejection fraction in adults with Friedreich ataxia

There is no RCT data regarding the treatment of either asymptomatic people with FRDA with reduced LVEF or of individuals with FRDA and with HF associated with reduced LVEF (HFREF). However, in the absence of any evidence for any FRDA disease-specific harmful effects of standard HF treatments it is reasonable to use current ACC/AHA Heart Failure Guidelines as a guide to therapy in FRDA, recognizing at the same time that there could be differences in the pathophysiology of FRDA heart disease The fundamentals of medication management for symptomatic HFREF are provided in the 2009 Focused Update of the 2005 AHA/ACC Guidelines for the Diagnosis and Management of Heart Failure in Adults (31).

Diuretics (most commonly loop diuretics) are recommended to manage symptoms and signs of fluid overload and will be required in most individuals with symptomatic HFREF (31).

Angiotensin converting enzyme inhibitors (ACEI) have been shown to reduce morbidity and mortality in studies of subjects with reduced ejection fraction whether or not there was a history of HF (31). The ACEIs which have been shown in RCTs to reduce morbidity and/or mortality in HF are captopril, enalapril, lisinopril, ramipril, and trandolapril. Further preference may be given to those which have been given once (lisinopril, trandolapril) or twice daily (enalapril, ramipril) rather than three times daily (captopril) in those trials. An ACEI should be started at a low dose and slowly titrated toward the maximal recommended dose unless there are intolerable adverse effects. An ACEI is not appropriate in individuals with a history of angioedema or anuric renal failure during previous use, individuals with symptomatic hypotension or pregnancy (31).

If an ACEI cannot be tolerated because of cough or angioedema then an angiotensin II receptor blocker (ARB) is an alternative. ARBs are not more effective than ACE inhibitors and the evidence for their benefit in HF is not as strong as the evidence for ACE inhibitors (31). The ARBs for which there is most evidence in RCTs in HF are candesartan and valsartan.

Long-term treatment with beta blockers can lessen the symptoms of HF and improve the clinical status of patients (31). In addition, like ACEIs, beta blockers can reduce the risk of death and the combined risk of death or hospitalization in HFREF. Three beta blockers have been tested and found to be effective in RCTs (long-acting metoprolol, carvedilol and bisoprolol). Beta blockers should be considered for all individuals with stable HFREF unless there is a specific contraindication to their use or an individual is unable to tolerate treatment with these drugs. Beta-blockers may be considered in people who have reactive airway disease or asymptomatic bradycardia but should be used with great caution or not at all in individuals with persistent symptoms of either condition.

Treatment with a beta blocker should be initiated at very low doses, followed by gradual increments (generally 2 week intervals) in dose if lower doses have been well tolerated. Patients should be monitored closely for changes in vital signs and symptoms during this up-titration period. As with ACEIs, the dose of beta blockers in controlled clinical trials was not determined by a patient's therapeutic response but was increased until the patient received a prespecified target dose. Low doses were prescribed only if the target doses were not tolerated, and thus, most trials did not evaluate whether low doses are effective.

Spironolactone is an aldosterone blocker which has been shown in a RCT to reduce mortality and the need for hospitalization in people with a LVEF <35% and either stage IV NYHA HF or stage III HF with a history of stage IV HF (400). In this study, low dose spironolactone was combined with an ACEI and a loop diuretic, with or without digoxin. Eplerenone is another aldosterone blocker which has been used in HFREF and has fewer endocrine side effects than spironolactone. In a RCT of individuals with NYHA class II heart failure and a LVEF <30% there was a reduction in mortality and hospitalizations for HF in the group treated with eplerenone in addition to standard HF therapy (401). More than 80% of the subjects were taking a diuretic, an ACEI and a beta blocker.

Digoxin is a drug with positive inotropic effects which can result in symptomatic improvement in HF but does not have any benefit on mortality (31). It can be considered in individuals who remain symptomatic after dose optimization of diuretic, ACEI and beta blocker. Digoxin may have a larger role in HF associated with AF to aid in rate control, particularly if beta blockers are contraindicated or if the ventricular response remains elevated despite the maximum tolerated dose of the beta blocker. Limitations of digoxin are its narrow therapeutic window and the necessity of renal excretion, the latter often reduced in end-stage HF.

Practical details about the commencement and maintenance of medications in HF are described in 2009 Focused Update of the 2005 AHA/ACC Guidelines for the Diagnosis and Management of Heart Failure in Adults (31) and also by McMurray and colleagues (402).

3.1.4.5 Pharmacologic treatment of heart failure in children with Friedreich ataxia and reduced left ventricular ejection fraction

There are no RCTs which have investigated the treatment of reduced LVEF with or without HF in children with FRDA. Neither is there even much data available from trials in children with HF due to a cardiomyopathy with reduced LVEF and causes other than FRDA. This is due in part to the difficulty performing RCTs in children given the low prevalence of pediatric HFREF. Treatment of HFREF in children has been based on the results from adult studies and this has been justified by the findings of similarities in

neuro-hormonal changes, (403-405) and systemic ventricular remodelling in the two age groups (406). In 2004, the International Society of Heart and Lung Transplantation (ISHLT) published guidelines for the treatment of HFREF in children which was primarily based on the adult literature (407). There is believed to be a role for diuretics, ACEI, digoxin and possibly for beta blockers in pediatric HFREF. However, a 2009 Cochrane review of beta-blockers in children with HFREF concluded there were not enough data to either recommend or discourage their use (408).

3.1.4.6 Lifestyle factors and cautions to aid in management of heart failure in Friedreich ataxia

Lack of physical activity, poor diet, excessive consumption of salt and fluids and being overweight can exacerbate HF. Exercise-based rehabilitation can lead to reductions in hospitalizations for HF and improved quality of life and does not increase mortality in people with stable HF (see section 2.5). Individuals who are requiring diuretics should generally be on a fluid restriction of less than 2L/day and more strict fluid restrictions may be necessary depending on the severity of the heart failure, the sodium level and the required doses of diuretics.

Some medications are known to increase the risk of HF and should generally be avoided in individuals with reduced LVEF with or without a history of HF. These medications include: conventional and COX-2 selective non-steroidal anti-inflammatory medications, thiazolidinediones (rosiglitazone and pioglitazone) and corticosteroids.

3.1.4.7 Device therapy for heart failure in Friedreich ataxia

Prolongation of the QRS interval occurs in a proportion of patients with advanced heart failure and has been associated with ventricular electromechanical delay (“dyssynchrony”) (32). QRS duration, dyssynchrony of contraction, and left bundle branch block in particular, have been identified as predictors of worsening heart failure, SCD, and total mortality. Modification of ventricular electromechanical delay with multisite ventricular pacing (“biventricular pacing and CRT”) can improve ventricular systolic function, ameliorate functional mitral regurgitation, and, in some patients, induce favorable remodeling with reduction of cardiac chamber dimensions. Individuals with FRDA can develop HF due to severe systolic LV systolic dysfunction and can have a LBBB so cardiac resynchronization therapy (CRT) should be considered in such circumstances.

Guidelines for CRT in patients with severe systolic heart failure are included in the ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities (32). For individuals who have LVEF less than or equal to 35%, a QRS duration greater than or equal to 0.12 seconds, and sinus rhythm, CRT with or without

an ICD is indicated for the treatment of NYHA functional Class III or ambulatory Class IV heart failure symptoms despite optimal recommended medical therapy (Level A Evidence).

3.1.4.8 Heart transplantation for heart failure in Friedreich ataxia

Transplantation of the heart in FRDA is not common but has been reported six times in the literature (409-412). Individuals with FRDA appear to do well after transplantation and no significant deleterious effects of immunosuppression have been noted apart from prednisone induced diabetes (410). There are no reports in FRDA of use of the newer immunosuppressive agents, such as tacrolimus or sirolimus which decrease oxidative phosphorylation in isolated mitochondria (413). In several transplanted individuals, there was either an improvement in or arrest of the FRDA neuromuscular findings for prolonged periods of time (409, 410). This raises the possibility that HF may contribute to the decrease in muscle strength and ataxia in FRDA. Important considerations for transplant in FRDA include the predicted lifespan of the patient, which in most cases would be expected to exceed the life of the transplant (412), and the degree of associated co-morbidities, such as severe scoliosis causing respiratory compromise. It is recommended that individuals with FRDA should be considered for heart transplantation if they experience severe heart failure which does not respond to maximal medical management.

3.1.4.9 Fluid and operative management of individuals with Friedreich ataxia with and without heart failure

The increased thickness of the left ventricle in FRDA results in a reduction in coronary flow reserve and less tolerance to tachycardia. The reduced size of the LV cavity in FRDA means a greater reliance on heart rate to maintain cardiac output and a reduction in stroke volume reserve. Hearts of individuals with FRDA will therefore have less tolerance for changes in hemodynamics such as bradycardia, tachycardia, low blood pressure, and increases or decreases in LV filling. Careful monitoring of fluid balance is essential in individuals with FRDA undergoing stressful events, such as scoliosis surgery or hydration therapy in the emergency room setting. In addition, rapid access to advanced technologies for supporting cardiac output following major surgery, such as dialysis and left ventricular assist devices, may be required.

3.1.5 Routine and perioperative cardiac assessment in Friedreich ataxia

It is recommended that all individuals with a diagnosis of FRDA have an EKG and echocardiogram performed as part of their initial evaluation and that the EKG and echocardiogram are repeated at least yearly thereafter, irrespective of the initial findings. Cardiology consultation should be considered for all individuals with FRDA but

is definitely indicated if there are cardiac symptoms or an abnormality on the echocardiogram.

Individuals with FRDA undergoing major surgery, such as scoliosis repair, should undergo EKG, echocardiography and cardiology consultation within a reasonable time frame prior to the surgery (e.g., 2–4 months prior) to evaluate LV structure and LVEF. Because of the increased risk of cardiovascular instability and complications during major surgery in FRDA, a multi-disciplinary approach to evaluate and manage these patients during and after surgery is recommended. This may include consultation and collaboration between the cardiologist, anaesthesiologist, intensivist and surgeon. Access to an intensive care unit capable of supporting a patient with severe HF is also recommended.

3.1.6 Pregnancy and heart failure in Friedreich ataxia

Women with FRDA can have uncomplicated pregnancies that do not necessarily lead to deterioration in disease-related symptoms, although this may at least partly reflect an inherent selection bias in those who become pregnant (43) (see section 8). There is little data available about pregnancy in women with FRDA and reduction of LVEF who are either asymptomatic or have HF symptoms. Based upon data in other cardiac conditions (414), it should be assumed that there is a high risk of maternal and fetal complications in women with FRDA and either reduced LVEF or a history of HF; therefore, avoidance of pregnancy should be recommended in such individuals.

3.1.7 Conclusions

Although significant advances have been made in understanding the molecular biology of FRDA, there remain substantial and fundamental gaps in our understanding of the clinical disease and natural history of FRDA. Furthermore, there are no RCTs of the treatment or prevention of arrhythmias or the treatment of HF and no trials which show any benefit of treatment to delay the onset of or prevent the development of left ventricular dysfunction in FRDA.

In view of the limitations of the available literature the following cautious recommendations are made:

1. All individuals with FRDA should have regular testing (at least annual) with EKG and echocardiography and should be seen by a cardiologist if cardiac testing is abnormal or if cardiac symptoms are reported. Either 24 hour Holter monitoring or Loop monitoring or possibly both tests are indicated for subjects with palpitations or other symptoms suggesting the possibility of an arrhythmia. A Loop monitor will be an appropriate additional test when symptoms are infrequent.

2. Patients with FRDA being considered for scoliosis surgery, or other major surgery, are at risk of poor outcome and require a multi-disciplinary approach to the management of heart function during surgery and in the postoperative period.
3. For treatment of symptomatic arrhythmias in FRDA, antiarrhythmic medications which are negatively inotropic or are recognized to have a high risk for proarrhythmic effects cannot be assumed to be safe and should rarely, if ever, be used.
4. There is no therapy with proven cardiac benefits for asymptomatic people with FRDA with echocardiographic or cardiac magnetic resonance findings of either a normal heart or increased left ventricular wall thickness but normal ejection fraction.
5. In adults with FRDA and a reduction in left ventricular ejection fraction there is a case for treating with an angiotensin converting inhibitor or an angiotensin 2 receptor blocker (if an ACEI is not tolerated due to cough) in an effort to slow or prevent further deterioration of LV contraction. There is also a case for consideration of a beta blocker, particularly in the setting of progressive deterioration of LV contraction. It is recommended that medications in these classes which have been tested and shown to be efficacious in randomized controlled trials in individuals with similar cardiac morbidity but without FRDA be given priority.
6. In individuals with FRDA and symptomatic heart failure due to a reduction in left ventricular ejection fraction (HFREF), medications which should be considered include a diuretic to normalize fluid state, an ACEI (or ARB), and a beta blocker. Spironolactone or eplerenone should be considered for NYHA class 3 or 4 heart failure. The dose of the ACEI and beta blocker should be slowly and carefully titrated to the maximal recommended doses if tolerated. If spironolactone or eplerenone are added to an ACEI or ARB then careful monitoring of potassium levels during both commencement and continuation of treatment is important.
7. Women with FRDA and reduction in left ventricular ejection fraction should be advised that pregnancy could result in cardiac decompensation and greater fetal risk and that it is therefore advised against.
8. Treatment options such as ICD and heart transplantation are not contraindicated in FRDA but the appropriateness of such therapy requires careful consideration of the individual's functional status and their prognosis from non-cardiac morbidities.

3.1.3 Recommendations

Recommendations	Grade

Cardiac evaluation and non-drug therapy	
An EKG and an echocardiogram should be performed at diagnosis and then at least annually.	GPP
A Holter and/or Loop monitor assessment should be performed if an individual with FRDA has palpitations.	GPP
Evaluation by a cardiologist should take place if an individual with FRDA has cardiac symptoms or abnormal results on cardiac testing.	GPP
Evaluation by a cardiologist should take place prior to major surgery.	GPP
Cardiac monitoring should take place during major surgery.	GPP
Major surgery should ideally be conducted in a center with cardiac intensive care facilities.	GPP
Exercise therapy including structured aerobic exercise and light weights, is recommended.	GPP
Heavy weight training is not advised.	GPP
Pharmacological therapy for slowing or prevention of deterioration of left ventricular contraction in asymptomatic individuals with reduced ejection fraction	
An angiotensin converting enzyme inhibitor (enalapril, ramipril, lisinopril or trandolapril) is first line therapy but if the angiotensin converting enzyme inhibitor is not tolerated then an angiotensin 2 receptor blocker (candesartan, valsartan) should be commenced instead (second line therapy).	C (31)
Beta blockers (carvedilol, bisoprolol or long acting metoprolol) should be considered as an addition to an angiotensin converting enzyme inhibitor or angiotensin 2 receptor blocker, particularly if the heart rate is >75/min.	GPP
Pharmacological therapy for treatment of symptomatic heart failure with reduced LV ejection fraction	
A diuretic should be prescribed for fluid overload.	C (31)
An angiotensin converting enzyme inhibitor (enalapril, ramipril, lisinopril or trandolapril) is first line therapy but if the angiotensin converting enzyme inhibitor is not tolerated then an angiotensin 2 receptor blocker (candesartan, valsartan) should be commenced instead (second line therapy).	C (31)
Beta blockers (carvedilol, bisoprolol or long acting metoprolol) should be added (first line therapy) to the angiotensin converting enzyme inhibitor or angiotensin 2 receptor blocker, however the role of beta blockers in children is less clear.	C (31)
Spironolactone or eplerenone should be prescribed for individuals with New York Heart Association (NYHA) stage 3 or 4 symptoms	C (31)
Calcium channel blockers with negative inotropic effects (verapamil and diltiazem) should be avoided.	C (31)

Digoxin should be prescribed for control of ventricular response if atrial fibrillation is present.	C (31)
Device therapy for subjects with symptomatic heart failure and reduced ejection fraction	
Implantation of an automatic internal cardioverter defibrillator should be considered if left ventricular ejection fraction (LVEF) is < 35%, the individual has NYHA functional class 2 or 3 symptoms despite receiving optimal medical therapy, and the individual has a reasonable expectation of survival with good functional status for more than 1 year.	C (32)
Cardiac resynchronization therapy should be considered in individuals with LVEF of < 35%, sinus rhythm, a QRS duration > 0.12 seconds and NYHA functional class 3 or 4 symptoms despite receiving optimal medical therapy.	C (32)
Antiarrhythmic agents for prevention of recurrence of atrial arrhythmias	
Agents which can be considered for use in this setting are a beta blocker (metoprolol, bisoprolol or carvedilol), sotalol, dofetilide or amiodarone.	C (33)
Agents to be avoided include quinidine, flecainide, propafenone and disopyramide due to their negatively inotropic and/or pro-arrhythmic effects.	C (33)
Anticoagulation for adults with atrial arrhythmias	
Anticoagulation should not be commenced if the LVEF is normal and there are no other risk factors for thromboembolism.	C (33)
Anticoagulation with warfarin or one of the novel anticoagulants (dabigatran, rivaroxaban or apixaban) should be considered in paroxysmal or permanent AF if one $CHADS_2$ risk factor is present and is generally indicated if more than one $CHADS_2$ risk factor is present.	C (33)
Anticoagulation with warfarin or one of the novel anticoagulants (dabigatran, rivaroxaban or apixaban) is strongly recommended in paroxysmal or permanent AF if there is reduced LVEF.	C (33)
Antiarrhythmic agents for prevention of recurrence of ventricular arrhythmias	
A beta blocker (metoprolol, bisoprolol or carvedilol) should be used, but sotalol and amiodarone are second-line options if there is arrhythmia recurrence despite beta blocker use.	C (32)
Cardiac Transplantation	
It is recommended that individuals with FRDA should be considered for heart transplantation if they experience severe heart failure which does not respond to maximal medical management.	GPP

Table 8 $CHADS_2$ risk criteria for stroke in non-valvular atrial fibrillation (33)

	Score
Prior stroke or transient ischemic attack	2
Age>75 years	1
Hypertension	1
Diabetes mellitus	1
Heart failure	1

Table 9 Stages in the development of heart failure (31)

Stage	
A	At high risk for heart failure but without structural heart disease or symptoms of heart failure
B	Structural heart disease but without signs or symptoms of heart failure
C	Structural heart disease with prior or current symptoms of heart failure
D	Refractory heart failure requiring specialized interventions

Table 10 New York Heart Association stages of heart failure (399)

Stage	
1	No limitations with normal physical activity
2	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitations, dyspnoea or angina pectoris.
3	Marked limitation of physical activity. Less than ordinary activity results in symptoms.
4	Unable to carry out any physical activity without discomfort. Symptoms are present at rest.

3.2 Sleep

Author: Dr Michael Ho, Dr Louise Corben

3.2.1 Overview

Sleep is a natural part of life. The lack of appropriate quality and quantity of sleep can affect daytime alertness, psychological well-being and cause a myriad of physical illnesses.

Obstructive sleep apnea (OSA) is a relatively common condition that results in poor sleep quality with predominant symptoms of disruptive snoring, fragmented sleep and excessive daytime sleepiness (EDS). OSA is characterized by repetitive episodes of partial to complete obstruction of the upper airway during sleep. This is associated with multiple episodes of apnea, oxygen desaturation, arousals and sleep fragmentation.

The estimated prevalence of OSA among middle-aged adults, as defined by an apnea-hypopnea index (AHI) >5 events/hour in community-based studies is 24% in men and 9% in women (415, 416). However the prevalence of OSA syndrome (symptomatic adults with AHI >5 events/hour and EDS) is around 4% in men and 2% in women in the middle-aged population (415).

The risk factors for OSA include obesity (417), male gender (417), age (418), increased neck circumference (419), craniofacial abnormalities (420), hypothyroidism and acromegaly.

The consequences of OSA relate primarily to neuro-cognitive and cardiovascular effects. In untreated OSA, sleep is often disrupted by repetitive respiratory arousals with resultant EDS (421) than can impair alertness, cognitive function and quality of life (422). Such EDS can be objectively measured, which has been shown to be associated with increased rate of occupational accidents (423) and up to three times higher rate of motor vehicle accidents (424) than control subjects. Likewise, successful treatment of OSA with nasal CPAP can reduce the risk of motor vehicle accidents (425).

There is clear independent association between OSA and cardiovascular disease; especially with systemic hypertension (426, 427), congestive heart failure (428, 429),

coronary artery disease (428, 430), cardiac arrhythmias (431, 432) and cerebrovascular disease (428, 433).

3.2.2. Sleep disordered breathing in neuromuscular disorders

Sleep disordered breathing (SDB) consists of a range of clinical entities which include OSA, sleep hypoventilation syndrome, central sleep apnea (CSA) and Cheyne-Stokes respiration.

Studies on a range of neuromuscular disorders such as Duchenne muscular dystrophy, amyotrophic lateral sclerosis and myotonic dystrophy have revealed a range of SDB (434, 435). The most common was REM-related hypoventilation, but OSA and CSA were also reported (434, 435). Recent studies on multiple sclerosis have documented the presence of SDB and its association with fatigue (436). Most studies have concluded that the treatment of SDB in patients with neuromuscular disorder may improve survival and quality of life (437).

3.2.3 Sleep disordered breathing in Friedreich ataxia

There is limited data in relation to SDB among people with Friedreich ataxia (FRDA). Botez et al (438) published a case report of an individual with FRDA, who had periodic breathing and mild OSA in a polysomnography (PSG). Another study by Manni et al (439) reported the results of PSG on nine individuals with hereditary ataxia, three of whom had FRDA. There was reduced REM sleep in all individuals, but SDB was detected in those with FRDA. Reddy and Grewal (440) documented a 41 year old woman with FRDA who had moderate OSA and CSA.

Fatigue is often reported by individuals with FRDA as having a significant detrimental effect on their quality of life (114). Fatigue often affects their capacity to perform personal care activities, work related tasks, participate in community or family life, or responsibly manage their health and interpersonal issues. As Kaminska and colleagues (436) has implicated the link between fatigue and SDB in patients with multiple sclerosis, a similar link may exist in those with FRDA. Moreover SDB, in particular OSA, has been associated with excessive daytime sleepiness (EDS) and cardiovascular co-morbidity including arrhythmia (441), which is frequently present in FRDA.

According to recently published data in Australia, there is a greater prevalence of SDB among those with FRDA. In a cohort of 82 individuals with FRDA, there was a minimum prevalence of 20% as compared to 3 – 7% in the general population (34). Surprisingly both central sleep apnoea and nocturnal hypoventilation were rarely seen. In this study those individuals with FRDA and proven OSA had longer disease duration and greater disease severity. Unlike the general population, there was no significant correlation

between OSA with male gender, obesity or Epworth Sleepiness Scale score (421). Hence the major risk factor for developing OSA appears to be the presence of advanced FRDA.

The mechanism underlying SDB in individuals with FRDA is still unclear. Gaig and Iranzo (437) suggested that SDB in the hereditary ataxias may be related to vocal cord abduction palsy. Changes in pharyngeal muscle activity, in addition to reduction in upper airway volume and protective reflex contribute to upper airway collapse characteristic of OSA. Those individuals with greater disease duration are more likely to have reduced vocal motor control which in turn may contribute to the presence of OSA. It is highly likely that these people have reduced respiratory muscle strength in conjunction with scoliosis and poor posture all of which may also contribute to the presence of OSA (34).

3.2.4 Assessment of sleep disordered breathing Friedriech ataxia

Screening for SDB in FRDA should include administration of the ESS and clinical assessment (442).

The Epworth Sleepiness Scale (ESS) is an eight item self-administered validated sleep questionnaire, which is often used as a clinical screening tool for OSA (421). Each item on the questionnaire reflects daily scenarios in which the possibility of dozing is rated on a scale from 0 (being no chance of dozing) to 3 (being high chance of dozing). As one such item relates to driving a motor vehicle, there is a potential bias to under-score for those individuals with severe FRDA who no longer drive. In the general population, individuals with OSA often have ESS scores above 10. As such individuals with FRDA with an ESS >8 may require further investigation for the presence of SDB (34).

Clinical assessment including questions regarding snoring, apneas as reported by sleeping partner or other members of the household and excessive daytime sleepiness may also be indicators of OSA.

3.2.5 Treatment of OSA in Friedreich ataxia

The most effective treatment for OSA is nasal CPAP (443, 444); whereby positive pressure is applied to splint the upper airway open. CPAP is generally recommended for individuals with severe OSA, mild-to-moderate OSA with severe symptoms and to those with medical co-morbidities. CPAP therapy in individuals with OSA, regardless of source of origin, has been shown to reduce mortality from cardiovascular disease (445) and ischaemic stroke (446). Mandibular advancement splint (MAS) is recommended for those with mild-to-moderate OSA, supine related OSA, retrognathia, or those who failed CPAP (447). Regardless of the severity of OSA, general measures are recommended which include weight loss, maintaining regular sleep-wake cycles, avoiding alcohol and strong sedatives before sleep.

Clinicians, caregivers and individuals with FRDA should be aware there is increased prevalence of OSA as disease progresses. In addition there should be a lower threshold for indication of referral to a Sleep Physician and polysomnography. Earlier diagnosis and appropriate therapy, which may include CPAP (35) can improve sleep quality as well as possibly improve quality of life and survival in individuals with FRDA.

3.2.6 Future research directions

Further studies are required to identify whether OSA accelerates fatigability, neuromuscular deterioration and underlying cardiomyopathy in individuals with FRDA. It is essential to establish if the instigation of CPAP can reverse these symptoms. In addition it is important that the significance of related clinical markers of increased risk of SDB such as neck circumference, bulbar function and pulmonary vital capacity is established in individuals with FRDA.

3.2.7 Recommendations

Recommendations	Grading
Clinicians, caregivers and individuals with FRDA should be aware there is increased prevalence of obstructive sleep apnea (OSA) as FRDA progresses.	C (34)
Annual evaluation of presence of sleep disordered breathing may be undertaken by administering of the Epworth Sleepiness Scale and reporting of clinical symptoms.	C (34)
For individuals with FRDA there should be a lower threshold for referral to a Sleep Physician and for polysomnography.	C (34)
Nasal continuous positive airway pressure therapy should be considered in the treatment of OSA.	C (35)

3.3 Pain management and anesthesia

Authors: Dr. Kelly L. Sullivan, Dr. Theresa A. Zesiewicz

3.3.1 Overview

Individuals with FRDA can experience pain from a variety of disease-related symptoms including neuropathy, spasms, cardiac and orthopedic issues.

3.3.2 Review of the literature regarding pain management and anesthesia in Friedreich ataxia

There are no systematic evaluations of the prevalence, severity or management of pain associated with FRDA and few case reports. Often, pain relief is achieved through treatment of the underlying cause – e.g. treatment of orthopedic issues or muscle spasms. Cardiomyopathy is common in people with FRDA and chest pain can occur due to abnormal coronary vasculature (448). One person presented with chest pain as the first symptom of FRDA at age 9 followed by a diagnosis of FRDA six years later (449) (see Section 3.1 on cardiology). Spasticity can contribute to pain in individuals with FRDA. One individual without clinical signs of spasticity was reported to have frequent painful extensor and flexor spasms that severely interfered with his quality of life (151). These spasms persisted despite oral baclofen treatment but responded to intrathecal baclofen (see also Section 2.4 on spasticity).

Peri-operative pain management is a concern in managing people with FRDA. Surgeries and associated anesthesia may be required to treat cardiac, orthopedic and obstetric issues. However, diabetes mellitus, cardiomyopathy and compromised pulmonary function make anesthetic management challenging. While practice guidelines have not been established, there are case reports of successful anesthesia using Remifentanil and Propofol (450), Alfentanil and Propofol (451) and Isoflurane (452). Use of muscle relaxants has been reported with mixed results in individuals with FRDA with one report of hypersensitivity to Tubocurarine (453). A more recent report by Schmitt et al (454) described the response of two adolescent girls with FRDA to Rocuronium. In particular the clinical duration of Rocuronium for both girls was comparable to children without neuromuscular disease indicating successful anesthetic management (454). Other reports describe a normal or near normal response to various nondepolarizing neuromuscular blocking agents such as Tubocurarine, Atracurium and Vecuronium (36, 37). Schmitt and colleagues (454) recommended accurate assessment of neuromuscular block throughout anesthesia for individuals with FRDA. In the case of obstetrics, successful use of Fentanyl and Bupivacaine have been reported in a case of a vaginal delivery (455) and caesarian section (456) (see also Section 8 on pregnancy). More recently Ozgul and colleagues reported the successful anaesthetic management of a person who underwent posterior spinal fusion (457).

A related review of the effects of anesthesia in individuals with a variety of muscular dystrophies (which did not include people with FRDA) reported cardiac complications associated with inhaled anesthetics and post-operative rhabdomyolysis. The authors also recommended avoiding use of succinylcholine which has been associated with life-threatening hyperkalemia (458). It is considered this recommendation may also be applicable to individuals with FRDA.

Finally, changes to cardiac function in people with FRDA indicate the capacity to tolerate lower blood pressure and large fluid shift as may be associated with surgery and anesthesia may be compromised. It is important to carefully monitor fluid loss and cardiovascular function during extensive surgery in FRDA (351).

3.3.3 Recommendations

Recommendations	Grading
Consideration should be given to appropriate management of peri-operative pain in people with FRDA.	GPP
Consideration should be given to the use of nondepolarizing muscle relaxants, in particular accurate assessment of neuromuscular block throughout anesthesia.	D (36, 37)
Consideration should be given to avoiding risks associated with hyperkalemia.	GPP
There should be careful monitoring of fluid balance and cardiovascular function in people with FRDA undergoing anesthesia.	GPP

4. Scoliosis

Authors: Dr Louise Corben, Dr John Flynn

4.1 Overview

Scoliosis occurs in most individuals with FRDA (40, 459-461) with a high prevalence of double thoracic and/or lumbar curves. Scoliosis may be severe and progressive, that is occurring before the age of 10 years and exhibiting a curve greater than 60°; or less severe and non-progressive with a curve less than 40° (461). Allard and colleagues (39) describe a typical individual with FRDA as presenting with a right thoracic spinal deformity which is relatively stable with a Cobb angle of 24° between the ages of 10 and 15 however then increasing by 24° in the following 5 years in addition to developing a compensatory left lumbar curve. Subsequent studies reported scoliosis in FRDA may be a single thoracic curve however the more usual pattern is of double major curves (40, 460, 462). Most studies report the most rapid progression of scoliosis occurring between the ages of 10 and 16 corresponding to the age of puberty and associated with significant growth (39, 40). It should be noted that scoliosis related to FRDA does not always progress and therefore does not always require intervention (38, 461, 463).

The etiology of scoliosis in FRDA is still unclear. It does not follow the usual pattern associated with scoliosis of a neuromuscular origin such as muscular dystrophy or spinal muscular atrophy (461, 464). Muscle weakness has not been shown to correlate with progression in scoliosis in FRDA (461). Spasticity is a significant component of the motor pattern disturbance associated with FRDA and it is possible that spasticity and/or disturbed postural reflexes may have a role in the development of scoliosis associated with FRDA. This hypothesis, while yet to be confirmed, may be significant in considering non-invasive methods of managing scoliosis in FRDA.

4.2 Literature search regarding scoliosis in Friedreich ataxia

A literature search revealed twelve articles related to this question*. These articles dated from 1957 to 2012*. The majority of these studies were retrospective. Table 11 provides a brief overview of each article.

4.3 Investigation of scoliosis in Friedreich ataxia

The usual method of investigation is antero-posterior and lateral full spine radiographs either standing or supine. However, Allard and colleagues (39) suggest this may lead to inconsistent measurement and recommends the use of a rotational booth. The Cobb method (465) is used to determine the degree of curve. Pelvic obliquity is defined as the angle between a line joining both iliac crests and a line intersecting the middle of the pedicles of L4 and L5 on the posteroanterior view (461, 466).

4.4 Severity of scoliosis in Friedreich ataxia

More severe scoliosis is generally found in individuals who have an onset of FRDA prior to 10 years of age (57, 459, 461). An earlier age of onset of FRDA generally coincides with the rapid progression of scoliosis between the ages of 10 and 16 years hence this time is particularly critical in terms of monitoring and intervention.

4.5 Literature search regarding intervention of scoliosis in Friedreich ataxia

The goal of intervention in individuals with FRDA is to prevent progression of scoliosis, improve upright stability in those who are ambulatory, improve balance and reduce the reliance on external orthoses for postural control and pressure/pain relief in those who are non-ambulatory. In addition, prevention of secondary respiratory complications is a significant factor to consider in the management of scoliosis in FRDA (466). In both ambulatory and non-ambulatory groups, pain is a significant indicator for intervention and thus successful intervention may have a significant impact on quality of life in people with FRDA.

Most authors recommend observation of children with a curve between 20° and 40° however suggest if the curve progresses beyond 40º that intervention is indicated (40, 461). Intervention can be non-invasive such as the use of bracing in the ambulatory individual or the use of customized seating to limit progression of rotation and lateral deviation of the spine in non-ambulatory individuals. The efficacy of bracing in controlling deformity has been questioned (460), however bracing may be particularly valuable in the very young and compliant person with FRDA in order to slow down progression and delay surgical correction (38). Unfortunately bracing may interfere with ambulation and breathing and thus compliance may be an issue (39, 40, 460, 462).

Posterior or anterior fusion may be considered for progressive curves greater than 40° in the child who is still growing (39, 40, 461). Milbrandt and colleagues (460) recommend consideration of surgery when the curves approach 50°. Stricker and colleagues (467) expanded the criteria to include those individuals who experience significant loss of balance while sitting, poor control of the head and difficulty complying with orthotic devices. Piazzolla and colleagues (466) proposed indications for surgery as deformity causing functional problems (poor sitting balance, difficulties with hygiene), or impingement of the rib cage on the pelvis or a deformity that could progress to create any of all of these problems. It has been recommended that the fusion area extend from T2 to L3 or L4 and the instrumentation contoured to accommodate the usual thoracic kyphosis and lumbar lordosis (459, 460). However some individuals may benefit from a shorter fusion and those who are non-ambulatory may require a fusion to the pelvis. The decision to fuse and the nature of the fusion should be based on each individual case taking into consideration the severity of the deformity, mobility and associated risks (38).

In regards to specific techniques Shapiro and colleagues (459) described the use of Harrington or Luque rods, double sublaminar wires at each level, two cross-link plates and autogenous (spinous processes) and allogeneic bone graft (459). Stricker and colleagues (467) reported that surgical complications in individuals with FRDA are more frequent than in those with other etiologies. As such they recommend rigid fixation, immediate mobilization post-operatively and a two-step ventral and dorsal procedure in cases where the curve is >50°. Daher and colleagues (462) also reported 5/12 individuals developed complications post-operatively including one ambulant person who lost the capacity to ambulate and therefore suggested careful consideration of surgery in the still ambulant individual with FRDA. Piazaolla and colleagues (466) and La Rosa and colleagues (468) recommended use of Cotrel-Dobousset (CD) instrumentation based on segmentation of the curves which then improves angular correction. This technique requires a shorter operative time and reduces vascular and neurologic risks both intra-operatively and immediately post-operatively (469).

Cardiopulmonary assessment is essential prior to consideration of surgery to ensure cardiac function is not compromised during the procedure and in the post-operative phase (351) (see also cardiology guidelines).

In consideration of surgical management of scoliosis for individuals with FRDA, it is essential to consider issues related to complications and post-operative management. Some studies reported post-operatively immobilization in orthoses for periods from 3 to 15 months (40, 462). Moreover, significant intraoperative blood loss may compound pre-existing cardiopulmonary issues (351); hence it is critical initial post-operative care is in an intensive care unit (ICU). Therefore surgery should occur in a facility with an ICU for appropriate post-operative management. Complications related to loss of mobility, de-conditioning, infection, failure of the implants, cardiopulmonary issues or death were reported in most studies. Consideration should be given in each case as to the post-operative requirements and availability in terms of acute community based care and impact on life roles of the individual with FRDA (e.g. time off school, increase in level of dependency, possible deconditioning associated with post-operative recovery). While there is some evidence that physical therapy may slow the progression and/or improve Cobb angles in idiopathic scoliosis (470) there is no evidence that such intervention would be effective in individuals with FRDA.

4.6 Conclusion

The available literature largely supports the role of surgery in correcting scoliosis in individuals with FRDA who demonstrate a curve >40° and in whom presence of a curve has a significant impact on health, independence and quality of life. Bracing, while not proven to affect the prognosis of the deformity or the need for surgical correction, may be valuable in delaying surgical correction in the very young child. Extensive

preoperative evaluation with particular attention to cardiorespiratory function is critical when considering surgical correction. Posterior spinal fusion appears to achieve satisfactory correction with minimal complications (38).

*After this section was completed and prior to publication of these guidelines a review of the literature identified a further publication (469) which was subsequently included in the reference list.

4.7 Recommendations

Recommendations	Grading
Individuals with FRDA with a spinal curve between 20° and 40° and/or between the ages of 10-16 years should be observed for curve progression.	GPP
Bracing may not reduce or stop the progression of curves however may be valuable in delaying surgical correction in the young child.	D (38)
People with FRDA with a scoliosis >40° may be considered appropriate for surgical correction.	D (39, 40)
Consideration should be given to delaying surgical intervention in ambulant individuals with FRDA.	D (38)
All people with FRDA considered for scoliosis surgery require extensive pre-operative evaluation and planning regarding cardiac and pulmonary function.	GPP

Table 11 Summary of studies related to scoliosis in FRDA

Author(s), Year	Type of study	FRDA n =	Intervention	Outcome
Allard et al (39)	3 year retrospective	32	Examination of pathomechanics of spinal deformity in FRDA.	Recommendation of examination and intervention.
Cady et al (40)	Retrospective, case series (pre-post)	42	Non-operative and surgery.	Bracing not effective. Surgery is indicated for curves >40º.
Daher et al (462)	Retrospective, case series (pre-post)	19	Bracing and surgery.	Bracing not effective. Surgery is indicated for curves >40º.
Labelle et al (461)	Retrospective	78	Non-operative and surgery.	Observation of curves <40º; observation and surgical treatment for curves <40º and >60º; surgical treatment for curves >60º.
Garfin et al (463)	Retrospective	21	Bracing and surgery.	Bracing not effective. Surgery is indicated for curves with documented progression.
Shapiro et al (459)	Literature Review		Bracing and surgery	Bracing for ambulant individuals with curve >25º and <35º. Consider surgery for non-ambulant individuals with curve>40º.
Aronsson et al (464)	Retrospective	12	Comparison of shape of curve between children with cerebral palsy, FRDA and adolescent idiopathic scoliosis.	Curve of FRDA resembles that of adolescent idiopathic scoliosis and is not related to muscle weakness.
Stricker et al (467)	Retrospective, case series (pre-post)	5	Posterior fusion with a modified Luque technique.	Significant complications with FRDA. Rigid fixation and immediate post-operative mobilization particularly important. Recommend two-step ventral and dorsal procedure when

				curve is rigid and >50º.
Milbrandt et al (460)	Retrospective, case series (pre-post)	49	Spinal fusion (n= 16) and bracing (n=10).	Poor results with bracing. Fusion effective.
Piazzolla et al (466)	Retrospective, case series (pre-post)	1	Cotrel-Dubousset instrumentation.	Good correction of deformity.
La Rosa et al (468)	Retrospective, case series (pre-post)	2	Cotrel-Dubousset instrumentation.	Good correction of deformity.
Tsirikos et al (38)	Retrospective	31	No intervention, bracing and surgery.	Bracing may be useful in delaying surgical correction in young child. Posterior spinal fusion achieves and maintains good correction with minimal complications.

5 Diabetes Mellitus

Author: Dr Miriam Cnop

5.1 Overview

Diabetes mellitus is diagnosed when, on two separate days, fasting plasma glucose is ≥ 126 mg/dl (normal level < 100 mg/dl) or when the two-hour plasma glucose after a 75 g oral glucose tolerance test is ≥ 200 mg/dl (normal level < 140 mg/dl). Intermediate results are called impaired fasting glucose and impaired glucose tolerance, respectively (471). Recently, HbA1C, a measure that reflects chronic glucose exposure, has been accepted as an additional diagnostic criterion for diabetes with a threshold value of ≥ 6.5% (≥ 48 mmol/mol) (normal level < 5.7% or < 39 mmol/mol). Individuals with an HbA1C of 5.7 - 6.4% (39 - 47 mmol/mol) are at increased risk for diabetes.

Diabetes results from defects in insulin secretion, insulin action or both. Chronic hyperglycemia can lead to damage of the eyes, kidneys, nerves, heart, and blood vessels.

It has been known for more than a century that individuals with FRDA are at risk of developing diabetes. Reported incidence rates vary between 8 and 32% (57-59, 80, 82, 101, 472-476). This variability can, in part, be explained by the diagnostic tests that were used. In one study the incidence of clinically diagnosed diabetes in FRDA was 8%, but an additional 10% were diagnosed using oral glucose tolerance tests (472). In a review of fatal cases of FRDA by the same authors, the incidence of clinically diagnosed diabetes was 23% (82). It should also be kept in mind that the diagnostic criteria for diabetes changed considerably over time. In a recent study of 41 FRDA patients who did not have a pre-existing clinical diagnosis of diabetes, 49% of participants had impaired fasting glucose and/or impaired glucose tolerance, and 12% had diabetes (477), illustrating that this metabolic complication of the disease is common.

The development of diabetes was correlated with the frataxin GAA trinucleotide expansion size in some studies but not in others. Filla and colleagues found that mean expansion size is higher in patients with diabetes (80). Delatycki and colleagues found a non-significant trend for the GAA expansion size of the smaller allele to be greater in patients with diabetes (57). Individuals with diabetes had a significantly greater duration of FRDA and a lower age at onset (57). In other reports, diabetes was not correlated with the size of the GAA expansions (59, 99, 477, 478).

5.2 Natural History in Friedreich ataxia

Unlike cardiomyopathy, diabetes is rarely reported as the presenting symptom of FRDA (although see (394). Diabetes usually presented after the onset of the neurological symptoms, after a mean duration of around 15 years (58, 474). Diabetes often requires insulin from its

onset (479). In a number of cases, the first presentation of diabetes in FRDA was ketoacidosis, which may be fulminant (82, 480).

5.3 Current assessment/investigations in Friedreich ataxia

Glycosuria has been abandoned for the screening for other forms of diabetes, because of low sensitivity, and it should not be used in FRDA. Accepted means to detect common forms of diabetes include fasting plasma glucose and HbA1C measurements and oral glucose tolerance testing, the latter having a better sensitivity to detect early changes in glucose tolerance and allowing for an early diagnosis. Indeed, screening with fasting plasma glucose or HbA1C will miss identification of new onset type 1 diabetes in the majority of cases (481). Likewise, in FRDA impaired glucose tolerance was often detected in patients with normal fasting glycaemia (477, 482). The fairly rapid progression from chemical to clinical diabetes in one case suggests that FRDA patients with mild abnormalities of glucose tolerance should be regularly reassessed in order to detect deteriorating glycaemia (483). Fasting glycaemia should be measured at least once a year, but the frequency of follow-up can be increased in case abnormal glucose metabolism is suspected or detected. As mentioned above, fasting plasma glucose and HbA1C are rather ineffective markers for new onset diabetes (481); for improved sensitivity it is recommended that an oral glucose tolerance test is performed.

5.4 Current interventions/management in Friedreich ataxia

The treatment of common forms of diabetes is largely empirical. Because of the marked insulin deficiency in type 1 diabetes, oral glucose lowering therapies will often fail rapidly, and patients require insulin therapy. For type 2 diabetes, where relative insulin deficiency coexists with variable degrees of insulin resistance, the recommendations are to start with lifestyle changes, and add on metformin, insulin and/or sulfonylurea (484).

In FRDA, both insulin deficiency and insulin resistance have been implicated in the development of diabetes. As mentioned above, many case reports described ketoacidosis, the hallmark of absolute insulin deficiency (480). It was suggested that this insulin-dependent ketosis-prone diabetes was caused by non-autoimmune loss of the insulin-producing pancreatic beta cells (485). A few reports have described a decreased number of islets and beta cells in the pancreas (110, 477, 486). Other studies found no difference in glucose-stimulated insulin secretion in FRDA patients (473, 487), though diminished arginine-stimulated insulin release was reported (473). The oscillatory insulin secretion pattern was preserved in FRDA (488). Insulin resistance was shown to be present, at the whole body and cellular level (121, 477, 482, 489, 490). Most of these studies addressing the pathogenesis of diabetes in FRDA were conducted before the genetic cause of the disease was elucidated (85) and before important concepts in glucose homeostasis were established (491-493). One of these crucial concepts is that insulin secretion is tightly regulated by insulin sensitivity (491, 493), as in many classical endocrine systems. Under normal conditions, pancreatic beta cells increase insulin release as much as needed to

maintain normal glucose tolerance. Thus, to interpret the insulin secretory response of the pancreatic beta cell correctly, it needs to be adjusted for the prevailing insulin resistance (492, 494, 495). In a recent study, this approach identified pancreatic beta cell dysfunction as central for diabetes development in FRDA (477).

The existence of both insulin deficiency and insulin resistance in FRDA implies theoretically that interventions acting at both these levels could be used. Insulin sensitizing treatments include lifestyle changes to decrease excess body weight and increase physical activity, metformin and thiazolidinediones. Metformin decreases hepatic glucose output and thereby ameliorates fasting glycaemia. Because metformin and thiazolidinediones have been shown to inhibit complex I of the mitochondrial electron transport chain, these drugs should probably be used with caution in mitochondrial diseases (496, 497). Thiazolidinediones, or glitazones, are PPARγ agonists. They have been associated with increased risk of congestive heart failure (498), which may pose a particular problem in FRDA. Drugs that enhance insulin secretion include sulfonylurea, analogs of the incretin hormone glucagon-like peptide 1, and inhibitors of dipeptidyl peptidase IV, the enzyme that degrades incretin hormones. Insulin therapy is the oldest treatment for diabetes and the most effective. It can be used for any type of diabetes and has no adverse side effects apart from hypoglycaemia. Unfortunately, there have not been any studies comparing efficacy of different diabetes therapies in FRDA.

Many of the earlier reports of diabetes in FRDA described severe ketosis-prone insulin-dependent diabetes (485, 499). This may be due to late diagnosis, when all adaptive mechanisms in glucose homeostasis have failed. As for other forms of diabetes, it is recommended that a timely diagnosis is made and therapy is started before hyperglycemic decompensation. Recommended treatment interventions for diabetes in patients with FRDA consist of weight monitoring, dietary recommendations and hypoglycemic oral therapy (12), which was used in 25% of a series of diabetic patients (58). Most often, however, insulin was required for the treatment of diabetes (12, 82). In individuals with childhood onset of FRDA who subsequently developed diabetes, all required insulin (67). Different from patients with type 1 diabetes who often experience a honeymoon period, FRDA patients do not have remission of diabetes after initiation of insulin therapy. Their insulin requirements approached 1 U/kg body weight (485).

As for other forms of diabetes, HbA1C can be used to monitor diabetes control in FRDA (500).

5.5 People with Friedreich ataxia are at risk of developing diabetes

In a review of cases with FRDA and diabetes, Podolsky and Sheremata identified a female preponderance, with more than two-thirds of patients being female (499).

In patients with childhood onset of FRDA (before age 10 years), the incidence of diabetes (25%) was greater than that of later onset patients. In this childhood onset group, the average age at onset of diabetes was 21 years (67).

Diabetes in FRDA has been shown to cluster within families (58, 499, 501); the risk of an individual with FRDA developing diabetes if an affected sib has it exceeds 40% (58).

5.6 Recommendations

The recommendations for diagnosis and therapy of diabetes in FRDA are essentially consensus-based; evidence-based guidelines need to be developed. The main goals of diabetes treatment in FRDA are to avoid hyperglycemic decompensation and prevent the development of chronic micro- and macrovascular complications*. Specific goals for the degree of glycemic control have not been established. Until more scientific data become available, this should be evaluated on an individual basis, taking into account life expectancy of the patient. Evidence for the described diabetes therapies comes from the treatment of other forms of diabetes. Safety has not been studied in FRDA for therapies other than insulin.

Recommendations	**Grading**
HbA1C may not be a good screening/diagnostic test in FRDA as it is not recommended in young individuals and in people in whom diabetes may present acutely.	GPP
Blood glucose should be measured at least once a year	GPP
Oral glucose tolerance tests have a better sensitivity than fasting plasma glucose or HbA1c to detect early changes in glucose metabolism, and enable earlier diagnosis of diabetes.	GPP
Diabetes treatment should be initiated early.	GPP
Lifestyle changes (diet and exercise) should be implemented in all with diabetes.	GPP
Insulin therapy should be initiated if diet and exercise alone do not achieve glucose control.	GPP

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***Addendum**: Please refer to a recent review on this topic by Cnop and colleagues (502)

6 Genetic Issues

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6.1 Overview

In this section the genetic aspects of FRDA are described and issues related to genetic counseling are discussed with guidelines for this process detailed.

6.2 Description of Friedreich ataxia

FRDA is an autosomal recessive disorder. About 1 in 30,000 individuals of Caucasian origin are affected by the disorder and about 1 in 85 individuals from that ethnicity are carriers of a single mutation (503). Whilst by far most common in Caucasians, FRDA is also seen, albeit less commonly, in individuals from the Indian subcontinent, North Africa and the Middle East but is extremely rare among Southern Asians and those from other parts of Africa (244). The mean age at onset is 16 years, and is before 25 years in most cases with a reported range from 2–60 years.

The gene in which mutations occur to result in FRDA was originally called *X25*, then *FRDA* and is now known as *FXN* (85). The gene has seven exons (1-5a, 5b and 6). The most common transcript arises from exons 1-5a and produces a 210 amino acid protein called frataxin. In about 98% of mutant alleles there is an expansion of a GAA trinucleotide repeat in intron 1 of the gene. Normally there are 33 or fewer GAA repeats and in affected individuals there are 66 to more than 1000 repeats in both alleles (88). The other two percent of mutations are point mutations/deletions (150). There is only one report of individuals with FRDA due to point mutations on both alleles (Helene Puccio, personal communication, 2011). All other individuals affected by FRDA due to a point mutation/deletion are compound heterozygous for a GAA expansion and a point mutation/deletion. At the time of writing of this report, forty-five different *FXN* point mutations had been reported (504).

The intron 1 GAA expansion results in reduced production of structurally normal frataxin. Some point mutations and deletions lead to absent protein (e.g.: L106X) whilst others lead to impaired but not absent protein (e.g.: G130V). (See section 7 for further description of point mutations)

The *FXN* GAA repeat expansion exhibits intergenerational repeat instability. Maternal transmission may result in expansion or contraction of the repeat, whereas paternal transmission is almost always associated with contraction of repeat size (505, 506). It has been shown that GAA alleles from at least 34 repeats can be unstable during meiosis and can result in disease causing alleles in offspring (84, 88, 507). The smallest reported disease causing GAA repeat is 66 however it is possible that smaller alleles could result in disease (503).

6.2.1 Genotype-Phenotype Correlations

The size of the smaller of the two GAA expansions is inversely correlated with age at disease onset, the presence of cardiomyopathy, diabetes mellitus and scoliosis (59, 80). The smaller allele accounts for about 50% of the variation in age at disease onset.

6.2.2 Genetic testing to make the diagnosis for Friedreich ataxia

Because one mutation accounts for the vast majority of FRDA, a simple and inexpensive test can diagnose most affected individuals. There should be a low threshold for undertaking this test on any individual in whom the diagnosis is considered. The phenotypic spectrum should be kept in mind in considering FRDA in the differential diagnosis of individuals presenting with symptoms that could be due to this disorder (see section 1.4). If an individual is found to be homozygous for *FXN* GAA expansions, then the diagnosis of FRDA is confirmed. If only one expansion is identified then the diagnosis is possible but not confirmed. Sequencing of *FXN* should be the next step and if a point mutation or deletion is identified in addition to the expansion, then the diagnosis is confirmed. If no other mutation is identified then the two possible explanations are that the individual is a heterozygous carrier of a *FXN* mutation and has another diagnosis as an explanation for their presentation or that a second *FXN* mutation is present that has not been identified (for example a promoter or intronic mutation). If no GAA expansion is identified then FRDA is very unlikely. Sequencing of *FXN* can be carried out in an effort to identify homozygosity or compound heterozygosisty for point mutations but this is very unlikely to yield a diagnosis and is not recommended unless there is a very high clinical suspicion or as part of a research exercise. If a person has clinical features of FRDA and one or no *FXN* GAA expansions and no point mutation(s) have been identified, consideration should be given to measurement of lymphocyte frataxin levels. If frataxin levels are very low, then it is likely that the diagnosis of FRDA is correct and that *FXN* mutation(s) are present but are not identifiable but standard methods.

FXN is the only gene known to cause FRDA. A second locus FRDA2 that was reported (508) has now been shown to be ataxia with ocular motor ataxia type 1 due to mutations in *APTX* (509).

6.2.3 Genetic counseling upon diagnosis of Friedreich ataxia

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

1. Autosomal recessive inheritance and the genetic mechanism of FRDA.
2. The implications for other family members including:
    - (i) 1 in 4 risk of FRDA in sibs (existing and future).
    - (ii) Risk of FRDA for the offspring of the affected individual (generally relevant to older teenagers and adults).
    - (iii) Carrier risk and availability of testing for relatives.
    - (iv) Availability of reproductive options where both members of a couple are identified as carriers.

6.3 Discussion in relation to GAA repeat number

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 repeat sizes are on average associated with a more severe phenotype, that in an individual, this information cannot be used to accurately predict phenotype or prognosis.

6.4 Testing of sibs

The sibs of a person with FRDA are conceived with a 1 in 4 risk of having two *FXN* mutations and being affected. The risk for an individual sib however depends on their age at the time they are seen. If they are younger than the proband at their age of onset then their risk of having FRDA is essentially 1 in 4. If they are older, the risk can be lower if they are asymptomatic since the probability decreases as an individual becomes older and doesn't have symptoms. Even if the sib is many years older than the proband when that person developed symptoms, there remains a risk of disease as there can be marked differences in age of onset within the same family. This relates largely to where sibs inherit different size expanded *FXN* GAA repeats.

6.5 Testing of adult siblings of a person with Friedreich ataxia

The goal of carrier testing for adult siblings of a person with FRDA is to allow for future 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, and it should be emphasized that a carrier for FRDA is a healthy person at risk of transmitting the *FXN* mutation to future offspring. When an adult sib requests carrier testing, they should be informed that their risk of being a carrier at conception was 1 in 2 and if they are much older than their sib 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). They should be warned that there is a small chance that testing will identify that they have two *FXN* mutations and will at some point develop symptoms of the condition. They should have a thorough discussion about the pros and cons of such testing. They should be offered the opportunity to have 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. They should be offered psychological support if signs of FRDA are identified at this point. The absence of any clinical signs of FRDA means the risk of that person being diagnosed with the condition is low. If subtle symptoms are identified then the individual should be forewarned about the possibility that FRDA will be diagnosed and provided with appropriate psychological support. All carriers should receive follow-up genetic counseling to discuss testing of their

current/future partner, risks to future pregnancies as well as options for prenatal diagnosis and management.

6.6 Testing of minor siblings of a person with Friedreich ataxia

Carrier testing of children for autosomal recessive conditions for the purpose of reproductive planning is not generally recommended (510-514). 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. 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 (510). There are cases where exceptions to this general rule may be in the best interest of the minor and his or her family (511, 515), as in the case of an emancipated minor 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 (516). 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 whether or not to test being made on a case by case basis. The potential psychological and social risks should be discussed, and the adolescent should be encouraged to involve his/her parents in the decision process. A study of nine individuals who underwent predictive testing for adult onset disorders (six gene positive) did not identify adverse outcomes from the individual knowing their genetic status (517).

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, sibling(s) of an individual with FRDA may have inherited two mutated FXN gene copies but not yet have 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 provide a pre-symptomatic genetic test if this request was made together with the minor's parents (516). A review of current guidelines regarding this topic 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 (512-514, 518). 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 his/her 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 this guideline 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 he or she reaches adulthood, and the lack of effective treatments for FRDA that slow disease progression 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 ability of 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 for inherited forms of cardiomyopathy, which includes FRDA, is standard of care (519, 520). The desirability of a multidisciplinary approach to pre-symptomatic genetic testing in children for FRDA was suggested.

It is recommended that the following be considered for situations involving pre-symptomatic genetic testing for FRDA:

1. Each situation is unique and should be managed on a case-by-case basis; there is no evidence to support the routine provision or refusal of pre-symptomatic genetic testing for FRDA at this time (GPP).
2. If testing is requested (GPP):
   - (i) The family should be referred to a team with expertise in this field for discussion about the request.
   - (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) 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, and if necessary a bioethicist, should be considered.
   - (iv) All patients identified pre-symptomatically and their families should receive immediate post-test counseling and psychosocial support.

(v) All patients identified pre-symptomatically should be referred for appropriate neurological and cardiac surveillance.

(vi) Minors who have the maturity to do so, should be involved in the decision as to whether or not they are tested.

(vii) The utility of anti-oxidant therapies, such as idebenone, has not been evaluated in the pre-symptomatic population and there is no evidence to support routine use of these therapies in patients diagnosed pre-symptomatically at this time.

Evidence-based studies regarding the genetic and counseling needs of patients with FRDA and their families are urgently needed. This information, in addition to the discovery of biomarkers which may better define early disease stages, and advances in therapeutic trials for FRDA, is necessary for health care providers to decide whether or not to offer or provide pre-symptomatic genetic testing for FRDA.

Addendum: For further discussion on this topic see paper by Lowe and colleagues exploring the opinions of individuals with and parents of individuals with FRDA regarding pre-symptomatic testing of minors (521).

6.7 Testing of other relatives

Table 12 lists the risk of being a carrier and the risk of having an affected child for the affected individual and various relatives of individuals affected by FRDA. The calculated risk of having an affected child assumes that the tested individual's partner 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* is not recommended in this setting due to the very low probability of finding a mutation (by comparison the risk of having a child with cystic fibrosis for a Caucasian couple is 1 in 2,500) and the risk of finding an variant of unknown significance and the consequent anxiety that this will likely cause. A variant of unknown significance is a DNA sequence change where it cannot be determined if it is a disease causing mutation or a benign polymorphism. If the couple request sequencing to exclude as best as possible the presence of a point mutation, they should be made aware of the possibility of finding a variant of unknown significance.

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.

The following are the options that are available to couples where both are carriers of *FXN* mutations. It is recognized that some or all of these will not be available in some centers.

1. *Prenatal diagnosis*- this is generally by chorionic villus sampling. Here the chorion (part of the developing placenta) is biopsied under ultrasound guidance. This tissue contains the same genome as the fetus. Less commonly, the test for prenatal diagnosis will be an amniocentesis, where amniotic fluid is removed under ultrasound guidance, rather than CVS. If the fetus is found to have two *FXN* mutations, the couple has the option of pregnancy termination. If prenatal diagnosis is undertaken and the fetus is found to have *FXN* mutations in both alleles and thus is affected by FRDA and the pregnancy is not terminated, this is equivalent to predictive testing of a minor. The issues discussed in relation to this (above) are relevant to this situation and appropriate counseling in relation to this is required.

2. *Preimplantation genetic diagnosis (PGD)* - here IVF is undertaken whereby the mother's ovum is fertilized *in vitro* by the father's sperm using intracytoplasmic sperm injection. The resultant 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* mutations. In the case of FRDA due to GAA expansions, this is generally by an indirect linkage method since it is not technically possible to identify large triplet repeat expansions in DNA from a single cell. Only embryos with one or no *FXN* mutation are placed in the mother's uterus. The fact that the chance of pregnancy is as low as 20% for each PGD cycle should be discussed with the couple. Since PGD is less accurate than prenatal diagnosis, prenatal diagnosis is generally offered to couples following PGD.

3. *Donor ovum, sperm or embryo*- the use of donor gametes or embryos where the donor(s) are not carriers of a *FXN* mutation will greatly reduce the risk of a child being born with FRDA. If possible, it is critical that any donor(s) that donate gametes or embryos are tested for the *FXN* GAA expansion to ensure that they are not a carrier of this mutation and therefore that the resultant child is at low risk of FRDA.

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

Table 12 Carrier and risk for offspring for individuals with FRDA and their relatives.

Relationship to proband	**Risk of being a carrier**	**Risk of having 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

6.7 Patient population

The population to who these guidelines apply is detailed in the relevant sections.

6.8 Scientific basis on which the guidelines were developed

These guidelines are partly based on standard genetic counseling practice and partly on the consensus of the committee who produced the guidelines. There are no specific clinical studies that inform the practice of genetic counseling in relation to FRDA.

6.9 Future research directions

The major area where a clinical study is desirable is a study of the attitudes of individuals with FRDA and their families in relation to predictive testing of asymptomatic minors at risk of the condition.

6.10 Benefits of guideline

The benefits of accurate genetic counseling include informed decision making about testing for carrier status and reproductive options. It can also assist families in decision making around testing asymptomatic minors. The process can be of psychosocial benefit in dealing with the impact of being diagnosed (or a child being diagnosed) with FRDA. There are 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 very 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 but studies of testing in other conditions have found that this is rarely of major impact particularly if that person's partner is found to not be a carrier.

6.11 Support services required for recommendation

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.

6.12 Recommendations

Recommendations	Grading
Any individual in whom the diagnosis of FRDA is considered should undergo testing for FRDA.	GPP
Referral to a clinical geneticist or genetic counselor should be considered on diagnosis of FRDA.	GPP
Requests for pre-symptomatic genetic testing are best managed on a case-by-case basis; there is no evidence to support the routine provision or refusal of pre-symptomatic genetic testing for FRDA.	GPP
The committee did not reach consensus on the issue of whether it is appropriate to conduct presymptomatic testing in a minor. Where a request for presymptomatic testing in a minor occurs, the individual/family should be referred to a team with expertise in this field for discussion about pre-symptomatic genetic testing in which the risks and benefits of pre-symptomatic genetic diagnosis are put forward. The risks and benefits from both the child's and parents' perspectives should be carefully reviewed during the pre-test assessment.	GPP
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, and if necessary a bioethicist, should be considered.	GPP
All patients identified pre-symptomatically and their families would benefit from immediate post-test counseling and psychosocial support and referral for appropriate neurological and cardiac surveillance.	GPP
Minors who have the maturity to do so, should be involved in the decision as to whether or not they are tested.	GPP
There is no evidence to support routine use of anti-oxidant therapies, such as idebenone in patients diagnosed pre-symptomatically.	GPP
Carrier testing should be first undertaken on the closest relative.	GPP

7 Friedreich ataxia due to compound heterozygosity for a *FXN* intron 1 GAA expansion and point mutation/ insertion/ deletion

Author: Professor Martin Delatycki

7.1 Overview

Whilst ~96-98% of FRDA is due to homozygosity for *FXN* intron 1 GAA expansions, ~2-4% is due to compound heterozygosity for a GAA expansion on one *FXN* allele and a point mutation, small insertion and/or deletion or large deletion on the other (85, 101). In this section, the latter will be called "*FXN* compound heterozygosity".

The phenotype of individuals with *FXN* compound heterozygosity is very variable. For some, the phenotype is indistinguishable from "classical" FRDA due to homozygosity for GAA expansions and the management issues are identical. Other point mutations/deletions can lead to a milder, more severe or somewhat different phenotype to typical FRDA and this may mean that there are different management issues. Table 13 lists published mutations other than GAA repeat expansions and the phenotype associated with these. Drawing conclusions about the impact of most of these mutations is difficult because:

1. One or few individuals with the mutation are reported and where there is more than one individual reported with the mutation, they are often from the same family.
2. There is limited or no clinical data available for many of the mutations.
3. The size of the expanded *FXN* GAA repeat on the other allele is likely to be important in the phenotype.

A number of mutations have been reported in more than one family (see Table 9). These are c.3G-T (3 families), p.Gly130Val (6 families), p.Ile154Phe (4 families), p.Arg165Pro (2 families), p.Trp173Gly (5 families), c.157delC (6 families) and deletion of exons 4 and 5 (4 families). The only mutation that is relatively common for which sufficient clinical data is available to make specific comment is p.Gly130Val. There have been 12 individuals published with this mutation (101, 102, 128, 362, 522). The following can be concluded about this point mutation:

1. Lower limb spasticity is more prominent than typical FRDA.
2. Upper limbs are affected to a far lesser extent than lower limbs.
3. Cardiomyopathy is less commonly seen than in typical FRDA.
4. Dysarthria is not reported.

Table 13 List of *FXN* point mutations and deletions and the phenotype associated with each

	Mutation	Number*	Mutation type	Phenotype	Refs
1	c.1A-C	1	ic	Typical (LI)	(101)
2	c.1A-T	N/A	ic	N/A	(523)
3	c.2T-C	1	ic	Typical (LI)	(101)
4	c.3G-A	1	ic	Typical	(524)
5	c.3G-T	3 (3)	ic	Severe (onset 2 years) (LI)	(101, 525, 526)
6	p.Leu106 Ser	1	ms	Mild- slow disease progression	(527)
7	p.Leu106X	2 (1)	ms	Typical (LI)	(101)
8	p.Tyr118X	1	ms	Typical	(150)
9	p.Asp122Tyr	1	ms	Typical but retained knee reflexes (LI)	(101)
10	p.Gly130Val	12 (6)	ms	Atypical- lower limb spasticity common	(101, 102, 128, 362, 522)
11	p.Asn146Lys	1	ms	Typical	(528)
12	p.Ile154Phe	6 (4)	ms	Typical (LI)	(101, 150)
13	p.Trp155Arg	1	ms	Typical (LI)	(529)
14	p.Trp155X	1	ms	Typical	(530)
15	p.Leu156Pro	1	ms	Early onset (3 years) (LI)	(101)
16	p.Arg165Cys	2 (2)	ms	Atypical- brisk knee and upper limb reflexes, minimal upper limb ataxia	(362, 531)
17	p.Arg165Pro	2 (2)	ms	Atypical- brisk upper limb reflexes	(531, 532)
18	p.Trp173Gly	6 (5)	ms	Typical (LI)	(101, 150)
19	p.Leu182Phe	1	ms	Atypical- minimal upper limb ataxia	(362)
20	p.Leu182His	1	ms	Typical (LI)	(101)
21	p.His183Arg	1	ms	Typical (LI)	(101)
22	p.Leu186Arg	1	ms	Severe- onset 3 years with severe cardiomyopathy	(528)
23	p.Leu198Arg	1	ms	Typical (LI)	(533)
24	IVS1ds+5G-C	1	sm	Atypical- severe lower limb wasting, no dysarthria 39 years after onset	(531)
25	IVS3ds+1G-A	N/A	sm	N/A	(534)
26	IVS3as-2A-G	1	sm	N/A	(85)
27	IVS4ds+2T-G	1	sm	Typical	(362)
28	c.165+1G-A	1	sm	Atypical- symptoms of peripheral neuropathy predated ataxia	(141)
29	c.2delT	1	dl	Atypical- chorea,	(535)

				myoclonus	
30	c.11_12delTC	2 (1)	dl	Atypical- chorea	(536)
31	c.100delG	1	dl	Typical (LI)	(150)
32	c.104delC	1	dl	Typical (LI)	(150)
33	c.157delC	6 (6)	dl	Typical (LI)	(101, 150)
34	c.118delC	1	dl	Typical but early onset (3 years)	(530)
35	c.317delT	1	dl	Typical but early onset (3 years) (LI)	(537)
36	c.340_352del13	1	dl	Typical but early onset (3 years) (LI)	(537)
37	c.158insC	1	in	Late onset (34 years) (LI)	(101)
38	c.296insT	1	in	Late onset (29 years), upper limb reflexes present (LI)	(530)
39	c.202_205delGTCAinsTTG	1	indel	Typical but early onset (3 years) (LI)	(537)
40	c.371_376del6ins15	2 (1)	indel	Typical	(87)
41	deletion exon 5a	1	ld	Typical	(528)
42	deletion exon 4, 5	4 (4)	ld	Typical but early onset (3 years)	(86)
43	deletion exon 2, 3	1	ld	Typical	(86)
44	deletion exon 4	1	ld	Typical	(86)
45	deletion whole gene	1	ld	Early onset (2-3 years), chorea	(538)

*= number of individuals reported in the literature with the mutation (number of families represented where more than one individual has been reported with the mutation)
ic= initiation codon mutation; ms= missense mutation; sm= splice mutation; dl= deletion; in= insertion; indel= insertion/deletion mutation; ld= large deletion; LI= limited clinical information available; N/A= no clinical information provided

7.2 Management of individuals with FXN compound heterozygosity

For individuals with *FXN* compound heterozygosity where the phenotype is the same as typical FRDA due to homozygosity for intron 1 GAA repeat expansions, the management guidelines in this document should be followed. The main atypical phenotype seen in *FXN* compound heterozygosity is "spastic ataxia" where there is marked lower limb spasticity. Here the management is directed at treatment of spasticity (see section 2.4). It cannot be assumed that other features of typical FRDA are not present and therefore monitoring for other features should occur such as regular monitoring for cardiomyopathy (see section 3.1).

7.3 Recommendations

Recommendation	Grading
If a person compound heterozygous for a *FXN* GAA expansion and a point mutation/deletion has a similar phenotype to those with FRDA due to homozygosity for GAA expansions, they should be managed as per the guidelines in this document.	GPP
If spastic ataxia is the predominant phenotype, then the main management issue is that of spasticity and the guidelines for management of spasticity should be followed.	GPP
It should never be assumed that other features of typical FRDA will not be present (e.g. cardiomyopathy, diabetes) and therefore monitoring for these should take place.	GPP

8 Pregnancy

Authors: Ms Lisa S. Friedman, Ms Kimberly A. Schadt, and Professor David R. Lynch

8.1 Overview

This topic will cover the management of couples contemplating pregnancy, and the pre and postnatal care of women with FRDA including the delivery of the baby and care following birth. With medical advances such as improved cardiac care and other medical interventions, the average life expectancy of individuals with FRDA has significantly improved beyond the previously reported age of 37 years. As such, many females with FRDA are considering family planning and pregnancy. This guideline will provide specific guidance for practitioners caring for such individuals.

8.2 Literature review

Retrospective studies and case reports were identified as contributing the following guidelines (42, 43, 45, 46, 539).

8.3 Pre-Pregnancy Counseling and Family Planning Considerations

1. Genetic testing for partners- see Chapter 7.

2. Family planning considerations – A retrospective review of 31 women with FRDA who experienced pregnancy found that it was easier for women with FRDA to care for children in the earlier stages of the disease (43).

8.4 Pregnancy Management

Two studies have evaluated pregnancy in larger cohorts of women with FRDA. A short report by MacKenzie and colleagues (45) detailed 17 women with 17 pregnancies and a retrospective analysis by Friedman and colleagues (43) studied 31 women who had 65 pregnancies resulting in 56 live offspring.

From both studies, the following findings were reported:

1. **Spontaneous abortion** occurred in 13.8% of the Friedman cohort, a smaller percentage than the estimated incidence in the United States of America (540). The spontaneous abortions occurred at an average of 8.2 weeks gestation. There was no information to suggest any of the spontaneous abortions were related to FRDA and all women who experienced spontaneous abortion in the Friedman cohort had other successful pregnancies.

2. **Pre-term birth** occurred in 13% of the Friedman cohort. This was defined as babies born before 37 weeks gestation. In this study, the earliest baby was born at 35 weeks (considered a late preterm). In the Mackenzie study, all babies were born > 36 weeks gestation. In the general U.S. population, the rate of pre-term birth is estimated to be about 12% (541). Thus, the rate seen in the Friedman study is largely comparable.

3. **Impaired glucose tolerance** occurred in 12.9% of the Friedman cohort and 5.8% of the Mackenzie cohort. In each cohort, one woman developed gestational diabetes during pregnancy. The remaining women were managed with dietary modification. In the general U.S. population, the estimated incidence of gestational diabetes during pregnancy is reported to be as high as 18% (542). Thus, the numbers reported in FRDA patients appear to be lower than in the general population.

4. **Pregnancy-induced hypertension** occurred in 11.8% of the Mackenzie cohort and 1.9% of the Friedman cohort. In the general population, the estimated incidence during pregnancy is between 5-7% (543).

5. **Preeclampsia** occurred in 3.7% of the Friedman cohort and none of the Mackenzie cohort. In the general population, the estimated incidence during pregnancy is approximately 5% (544).

8.5 Friedreich ataxia Related Changes with Pregnancy

In the Friedman and colleagues (43) study, women were asked to retrospectively rate the changes in their FRDA they perceived during pregnancy. 28.6% of women felt pregnancy made their disease better, citing a feeling of improved balance and coordination. 35.7% of women felt pregnancy made their FRDA worse, most commonly experiencing increased fatigue, urinary urgency, speech, balance and coordination difficulties. 35.7% of women felt pregnancy did not alter their FRDA.

8.6 Recommendations for the Management of women with Friedreich ataxia during Pregnancy

1. **Glucose Tolerance Testing** – Individuals with FRDA are predisposed to the development of diabetes. Therefore, it is advisable that a woman's glucose levels be carefully monitored throughout pregnancy. As is standard with any pregnancy, glucose tolerance testing should be performed between 24-28 weeks of gestation (41) or earlier for individuals deemed to be at high risk by their practitioner.

2. **Cardiac Management** – Individuals with FRDA are predisposed to the development of cardiomyopathy, arrhythmias and other cardiac abnormalities. Thus, close monitoring by a cardiologist during pregnancy is essential.

3. **Neurologic Exam Testing** – Changes in the patient's FRDA disease status can be monitored prospectively by a trained physician using the Friedreich Ataxia Rating Scale (FARS) Exam or another suitable neurologic exam. This will allow for quantitative tracking of the neurologic disease changes that occur with pregnancy. One would not anticipate permanent changes in neurologic disease status as a direct result of pregnancy; however, women may experience transient changes which should be monitored and followed by a physician to assure that level of functioning and disease status return to pre-pregnancy state.

8.7 Managing Pregnancy Complications

When complications do arise, there are a few case reports in the literature detailing the management of these.

1. **Treatment of Preeclampsia** – One case study by Bruner and colleagues (539) described profound motor weakness and respiratory depression precipitated by the use of magnesium sulfate to treat preeclampsia. The authors hypothesized that magnesium may act synergistically with the underlying neuromuscular abnormalities found in FRDA to cause acute profound weakness. An alternative treatment may be phenytoin (42), although this has not been tried in any studies to date. ***There is insufficient evidence to determine if magnesium sulfate can be safely administered to preeclamptic FRDA patients. (Level of Evidence: IV)***

2. **Treatment of Pre-Term Labor** – Although beta-agonist tocolytic agents are often used in an attempt to arrest early labor, these agents may be problematic in women with FRDA due to underlying cardiac and/or endocrine pathologies. Some experts have speculated that Indomethacin may be one potential alternative although no research exists on this topic to date (42). ***There is insufficient evidence to determine if common beta-agonist tocolytic agents can be safely administered to women with FRDA experiencing pre-term labor. (Level of Evidence: GPP).***

3. **Treatment of Deep Vein Thrombosis –** One case study detailed the development of deep vein thrombosis (DVT) in a 23-year old gravida 3 para 1 female with FRDA at 34 weeks gestation (42). The patient was treated with Enoxaparin but went on to develop a pulmonary embolism. She had spontaneous vaginal delivery at 38 weeks. Upon birth, her infant was found to have two ventricular septal defects and coarctation of the aorta, which required surgical correction. The authors point out that during pregnancy, heparin is the mainstay of treatment for DVT as Coumadin crosses the placental membrane and is a known teratogen.

8.8 Delivery and the Post-Partum Period

In the Friedman cohort, 78% of births were vaginal, while 22.2% were cesarean sections, including 2 elective cesarean sections. The cesarean section rate was below the national average in the United States of approximately 25% (545). 87% of babies were born at term, with 13% born preterm (between 35-37 weeks).

In the Friedman cohort, the average birth weight of the babies was 7 lb 7.5 oz (3390g). 88.9% of babies were a normal weight, defined between 6 and 9 lbs (2720-4080g). 90% of newborns had an Apgar score between 7 and 10 at one minute after birth. All babies on whom data was available had an Apgar score between 7 and 10 at 5 minutes after birth.

From the Friedman cohort, the average length of hospital stay for the mother following delivery was 2.6 days. 94.4% of babies were discharged from the hospital with their mothers. Three babies had longer stays. One was febrile and spent two days in the NICU for transient tachypnea of the newborn. Another spent 10 days in the NICU for a small pneumothorax. Insufficient medical records were available to evaluate the cause of the third infant's prolonged hospitalization. In the United States, following uncomplicated deliveries, it is standard for mothers and infants to remain hospitalized for 48 hours following a vaginal delivery and 96 hours following a Caesarean section (546). Thus, the outcomes seen in women with FRDA follow the expected time trajectory.

Fetal distress was found as a complication in 7.4% of laboring mothers in the Friedman cohort. In the general population, it is reported to be approximately 2% (44). The reason for the elevation among the babies of women with FRDA is unclear. However, during delivery, it is imperative that the baby be closely monitored.

There are successful reports of both the administration of epidural and spinal anesthesia to women with FRDA during delivery (45, 46).

Following delivery, in the Friedman cohort, 50% of women believed their FRDA symptomatology did not change. 7.1% of women believed their disease improved, but could not specify the nature of improvement. 42.9% of women believed their FRDA became worse following delivery, citing increased fatigue, urinary urgency, and balance difficulties.

From the Friedman cohort, 52.4% of women said FRDA had a huge or moderate impact on their decision to get pregnant. 52.6% of women were concerned or extremely concerned about a shortened life expectancy because of FRDA. Many of the mothers in the study had to make special accommodations for their baby, such as buying wheel-chair accessible cribs. The majority of women felt that their children benefited from having a mother with a physical disability, saying their children were "more sensitive and caring towards the needs of others."

Despite the sensory and proprioceptive loss that occurs in FRDA, a vaginal delivery can still be expected of most pregnancies. The vast majority of babies born to mothers with FRDA are at healthy birth weights and can be expected to be discharged home with their mothers following the traditionally recommended length of stay (48 hours for vaginal delivery, 96 hours for

caesarean section). As women with FRDA are potentially at higher risk for fetal distress during delivery, close fetal monitoring during this stage is imperative. When cesarean section is medically indicated, epidural or spinal anesthesia can safely be used. In order to better quantify disease changes, the patient's FRDA disease status following pregnancy can be monitored prospectively by a trained physician using the Friedreich Ataxia Rating Scale (FARS) Exam or another form of neurological examination. Under normal circumstances, the pregnancy of a woman with FRDA need not be considered high risk. Women with FRDA should be encouraged to proceed with pregnancy if they wish to do so and if their cardiac status is adequate.

8.9 Future research directions

These guidelines have been developed using retrospective studies, case reports and expert opinion. In the future, larger, prospective studies following women with FRDA during their pregnancies, deliveries and post-partum care will allow for the development of more evidence-based guidelines.

8.10 Recommendations

Recommendations	Grading
The availability of testing for carrier status of reproductive partners should be made known to couples where one member has FRDA. If testing is requested, the carrier status of the unaffected partner should be established prior to conception in order to advise the couple of the risk of having a child with FRDA and to offer appropriate counseling.	GPP
When possible, it is advisable for women to have children earlier in their disease course.	GPP
Glucose tolerance testing should be performed between 24-28 weeks of gestation or earlier for individuals deemed to be at high risk by their practitioner.	D (41)
Women with FRDA should have close monitoring by a cardiologist during pregnancy.	GPP
Pregnant women with FRDA and deep venous thrombosis should be treated with heparin as opposed to warfarin.	D (42)
Vaginal delivery can be expected for most pregnancies in women with FRDA.	D (43)
Close fetal monitoring during delivery is recommended.	D (44)
If cesarean section is medically indicated, epidural or spinal anesthesia can generally be safely used in women with FRDA.	D (45, 46)

9 Quality of life

9.1 Overview of Quality of Life in Friedreich ataxia

Author: Ms Jennifer Farmer

Quality of Life (QOL) in FRDA is influenced by many different factors not the least of which is living with a chronic, progressive disease. Being able to quantify health-related QOL issues is essential to clinical research and long term evaluation of the impact of new treatments and guideline recommendations. This section will cover specific issues related to QOL in individuals with FRDA and in particular techniques and equipment that promotes health and independence in a person with FRDA and the presence and management of mental health and psychological symptoms related to FRDA. Specific attention is given to medical management in the later stages of the disease process when quality of life is the driving focus of medical decision making.

9.1.1 Literature Review of general Quality of Life in Friedreich ataxia

There are only a handful of studies specifically evaluating quality of life in individuals with FRDA. These studies and findings are presented in Table 14.

There is no doubt that FRDA is associated with decreased quality of life. The Australian and US studies have very similar findings utilizing the SF-36 to quantify QOL in a diverse cross-sectional cohort of adults with FRDA (114, 190). The SF-36, while not specific to FRDA, is able to capture QOL at various stages of disease (114, 190). While physical components have worse scores, both physical and mental components of health related QOL are also decreased in individuals with FRDA in various stages of disease (114, 190). Even those with milder stage and/or late onset FRDA reported decreased QOL (190). The results from these studies should signal to a clinician that from the point of diagnosis onward individuals with FRDA may have decreased quality of life which may impact on other aspects of life including psychological function. Any adjunctive support that can improve an individual's symptoms, especially physical symptoms such as reduced ambulation, fatigue or pain could improve quality of life. The later sections of this chapter will deal such approaches to adjunctive support.

In reviewing these studies it is important to note the range of instruments used to measure QOL in FRDA. The SF-36 in a range of versions has been used most often for adult participants (114, 190, 547). In pediatric cohorts the PedsQL has been used to assess QOL (115, 548). This instrument offers both child report questionnaires based on age and parental report questionnaire. In addition there has been research to develop a disease-specific instrument, the Friedreich's Ataxia Impact Scale or FAIS (549).

9.1.2 Recommendations

Recommendations	Grading
Adherence to the guidelines for managing FRDA may improve quality of life.	GPP

Table 14 Literature Review of general Quality of Life in Friedreich ataxia

Authors	Title	Type of Study	Participants	QOL Measures	Results	Conclusions
Riazi et al (547)	Coordinating outcomes measurement in ataxia research: Do some widely used generic rating scales tick the boxes?	Prospective; Observational; questionnaire mailed to individuals at T1 – baseline and T2 – 12 months later (97% response rate)	56 individuals with FRDA (57% female; mean age 31 years)	Barthel Index (BI), General Health Questionnaire (GHQ-12), EuroQOL (EQ-5D) and SF-36 version 1	Scores on individual measures were reported for subjects but not controls or population norms.	All four generic instruments used to assess QOL were found generally suitable but all had some limitations. The BI and EuroQOL has several missing data points and therefore are not recommended for this population. While the subscales of the SF-36 were able to capture multiple dimensions, some of the subscales had floor and/or ceiling effects in this population. Authors argue that a disease specific instrument is warranted.
Wilson et al (190)	Quality of life in Friedreich ataxia: what clinical, social and demographic factors are important?	Prospective; cross-sectional; data collected at time of visit	63 individuals with FRDA (15yrs and older; 54% female and 46% male, mean age 33 years)	SF-36 V2	SF-36 V2 scores were compared with Australian population norms. Physical Component Summary – mean score 35.1, P<0.01. Mental Component Summary – mean score 48.1, P<0.01.	QOL is significantly reduced in individuals with FRDA; physical dimensions of QOL being most affected. Individuals with mild, moderate and severe disease all perceived significantly worse QOL; including those with adult onset FRDA.
Epstein et al (114)	Health related quality of life measures in Friedreich ataxia	Prospective; cross-sectional; data collected at time of visit	130 adults with FRDA (72 females and 58 males; median age 33.5 yrs)	SF-36 (version 1 derived from the Multiple Sclerosis Quality of Life Inventory - MSQLI) and symptom specific	SF-36 scores were compared with US population norms. Physical Component Summary – 33.2 ±9.3, P<0.0001. Mental Component Summary	Both the SF-36 and symptom-specific HRQOL questionnaires captured QOL especially related to physical symptoms. The Physical Component Summary and Physical Functioning Subscale of the SF-36 correlated with measures of disease progression.

				scales used in the MSQLI (Pain, Fatigue, Bladder dysfunction, Bowel dysfunction and Visual Impairment)	– 51.9 ± 10.0. MSQLI – Subscales of Fatigue, Pain Bladder (all had P values< 0.0001) and Vision were lower in individuals with FA compared to controls.	
Cano et al (549)	Friedreich's Ataxia Impact Scale: A new measure striving to provide the flexibility required by today's studies	Prospective; cross-sectional; questionnaire mailed to individuals (69% response rate)	307 individuals with reported FRDA (18-82 yrs; 53% female and 47% male; average age 40 yrs)	Friedreich Ataxia Impact Scale (FAIS 126 item scale in full version with shortened versions for observational studies or for "more" or "less" severe cohorts).	Patient-reported rating scale quantifying eight areas considered clinically important to individuals with FRDA: Speech, Body movement, Upper limb functioning, Lower limb functioning, Complex tasks, Mood, Self-perception, and Isolation. Rasch analysis allowed for the development of three shorter versions of the FAIS.	This study validated a new FRDA-specific comprehensive measure in a large and diverse cohort of adult individuals with FRDA.
Paulsen et al (115)	Health-related quality of life in children with Friedreich ataxia	Prospective; Cross-sectional; data collected at time of visit	43 children with FRDA (8-18yrs; 21 male and 22 females; average age 13.2 yrs)	PedsQL 4.0 - 23 item, multidimensional questionnaire that has been validated in healthy and	Child Self Report: Generic Core Total - 66.4±14.7, P<0.0001. Physical Health Subscale – 63.2±17.4, P<0.0001. Psychosocial Heath	Children and parents both reported lower QOL compared to literature based control groups. Physical health scores were the lowest. PedsQL 4.0 captures aspects of health-related QOL across multiple dimensions and demonstrates modest correlation to

			and parents	chronic disease cohorts. A Generic Core Scale assessed four domains (physical, emotional, social and school) and subscale scores are derived for physical and psychosocial. Other symptom specific scales are available, such as fatigue which was used in this study.	Subscore – 68.1±16.2, P<0.0001. Fatigue Total Score – 72.8±15.3, P<0.01. Parental Report: Generic Core Total - 62.8±15.9, P<0.0001. Physical Health Subscale – 54.7±21.5, P<0.0001. Psychosocial Heath Subscore – 67.1±16.4, P<0.0001. Fatigue Total Score – 73.2±14.0, P<0.0001.	measures of disease severity in children with FRDA.
Brandsema et al (548)	Intermediate-dose Idebenone and quality of life in Friedreich ataxia	Prospective, observational study. Duration 1 year with use of Idebenone (no previous use of Idebenone in cohort).	7 children with FRDA (13-18yrs; 4 males and 3 females; average age 15.9 yrs)	PedsQL 4.0 (see description above), Activities of Daily Living – self-reported 11 item questionnaire that assesses function in nine categories.	PedsQL Child Self Report: Generic Core Total - Baseline - 46.43±19.45 and 1 yr 49.00±11.34. Physical Health Subscale – 35.57±25.95 and 1 yr 27.43±15.82. Emotional Subscale – Baseline 47.17±12.20 and 1 yr 53.57±15.20.	This study demonstrated the use of QOL and ADL instruments in a small observational study. The baseline scores are similar to those reported in other studies demonstrating decreased QOL in children with FRDA. This study is limited in size and had no control group so definitive conclusions cannot be made about the effect of Idebenone on QOL.

9.2 Mental Health issues

Author: Ms Jennifer Farmer

While psychiatric symptoms are not part of the presenting or diagnostic clinical features of FRDA, published literature and clinical experience indicate that many individuals with FRDA suffer from depression, anxiety and associated mental health issues.

9.2.1 Literature review of prevalence of mental health issues in Friedreich ataxia

A review of the literature on mental health illness, psychiatric conditions or depression in individuals with FRDA was conducted. Literature from the early 1900's suggested the presence of dementia and psychosis in individuals with FRDA however these reports were prior to clear diagnostic criteria and, in later publications thought to be complicated by misdiagnosis and selection bias (individuals reported were institutionalized and not a representative sample of individuals with the disease) (285, 286).

Flood and colleagues (285) reported their clinical experience and also a retrospective medical record review of 38 patients who met the clinical diagnostic criteria for FRDA and attended the Ataxia Clinic at University of California Los Angeles. They found that whilst dementia and severe cognitive disturbances were rare, most (92%) individuals with FRDA had mood disturbances, ranging from a mild, grief-related, reactive depression to severe depression. They concluded that the depression was a consequence of living with a chronic, progressively disabling, neurological disease rather than being intrinsic to FRDA. This report elegantly reminds the clinician of the likely psychological impact of living with a disease that causes continual loss of abilities, loss of livelihood and loss of future. The authors further suggest that what are initially normal responses of grief and depression can become prolonged and clinicians need to consider that individuals with FRDA may be at an increased risk for major depression and suicide (285). Giordani and colleagues (286) also examined the psychological status in individuals with FRDA and reported significantly higher levels of anxiety, depression and social isolation than in individuals without FRDA. Both these studies identified that FRDA not only affects the individual diagnosed with FRDA, but has a far-reaching effect to the entire family particularly the burden and loss that they will face over the prolonged course of the disease.

There are a few further publications of small cohorts that report the frequency of affective disorders in FRDA (291, 295, 297). White and colleagues reported neuropsychological and neuropsychiatric characteristics of 15 adults with FRDA (mean age 36.1 years). While finding some differences in performance on some cognitive tests, there was no difference in mood disorders when screened with the SCL-90 and Hamilton depression scale compared to age-matched controls. A few of the subjects with FRDA

did have a history of a past adjustment disorder with depressed mood. The authors specifically mentioned that one third of the individuals with FRDA demonstrated inappropriate jocularity during testing (291). Ciancarelli and colleagues (297) found that 29% of individuals with FRDA (24 adults) had mood disorders, mostly depression, when they assessed for cognitive disorders with a neuropsychiatric battery.

Mantovan and colleagues (295) administered the Minnesota Multiphasic Personality Inventory (MMPI) to eight adults with FRDA. In this small cohort, half of the individuals showed a profile outside the normal range. None of the control participants demonstrated similar profiles. The personality pattern of the individuals with FRDA was characterized by increased irritability, poor impulsive control, or blunting of affect. In addition, the subjects had low scores on the MMPI K scale and negative dissimulation index suggesting reduced defensiveness and a poor self-presentation. The authors point out that the significant physical disability associated with FRDA and having an onset in childhood and adolescence may play a significant role in the development of personality or lead to maladaptive behavior observed in this profile (295). Despite being a small cohort, the results of this investigation provide a fascinating insight into the little investigated area of personality changes related to FRDA.

More recent studies examining cognitive function in individuals with FRDA screened participants with and without FRDA for depression using the Beck Depression Inventory (BDI). The first two studies (302, 550) demonstrated significantly greater scores on the BDI in 13 -15 individuals with FRDA compared to 13-15 individuals without FRDA. Two later studies (222, 303) did not show a significant difference in BDI scores between 10-13 participants with FRDA and those without FRDA.

An exploratory study of transitional life events in individuals with FRDA highlighted that the usual transitional events in a person's life are exacerbated by the presence of FRDA. Moreover, such transitional events were accompanied by significant grief and loss associated with challenges to identify and self-esteem (189). As such it was not unusual to find a greater incidence of reactive depression in a cohort of individuals with FRDA compared to the control group. Indeed one recent study has specifically examined depression in individuals with FRDA in the context of neuroimaging (551). Twenty-two individuals with FRDA were screened for depression using the BDI and then cerebral 3T MRI scans to examine volumetric changes between individuals with FRDA and depression and those individuals with FRDA however without depression. A little more than a third (36.3%) of individuals with FRDA fulfilled the DSM-IV criteria for major depression. Whilst this incidence is higher than in the general population it is similar to reports in other neurodegenerative diseases (551). There was no correlation with age, disease severity or disease duration and the BDI score. The MRI studies showed grey matter atrophy in the frontal lobe of depressed individuals with FRDA. In addition, the severity of depression correlated with atrophy in the right superior frontal gyrus. The authors pointed out that it is not possible to know if long term major depression caused

the atrophy observed on MRI or if these changes are due to the neurodegenerative process of the disease (551).

9.2.2 Clinical Experience

To gain further insight into the prevalence of psychiatric conditions and mental health among individuals with FRDA we evaluated the reported frequency of psychiatric diagnoses from a large cohort of individuals with FRDA. The Collaborative Clinical Research Network (CCRN) in FA has a large multi-center natural history study ongoing with more than 600 individuals with genetically confirmed FRDA enrolled. At every visit subjects are queried for medical conditions both related and unrelated to FRDA and all subjects are examined by a physician and questionnaires on activities of daily living and quality of life are administered. Data is recorded into case report forms and entered into a central database.

In late 2012, a query of the database revealed that 576 subjects (children and adults) had completed the medical history questionnaire for at least one visit. From these subjects 256 psychiatric conditions were reported (single individuals could report more than one condition); more than half of those reported were depression. Of note, these are self-reported conditions and no formal testing or evaluation was done to confirm or clarify diagnoses.

Table 15 provides a summary of the conditions reported in this cohort. Some vague reports of mood disturbance, anger, panic disorder, flat affect, obsessive compulsive behavior and psychosis were omitted from the table; no subject had more than 3 reports.

9.2.4 Treatment

If depression and mental health issues are suspected in individuals with FRDA proactive management should include referral to appropriate clinicians, instigation of pharmacological therapy if indicated and referral for counseling. In particular, given the prevalence of depression in individuals with FRDA and impact on quality of life, clinicians should be vigilant to the possibility that depression may occur and provide swift and timely intervention

9.2.5 Conclusion

A clinician should expect grief and sadness in individuals with FRDA, particularly as they deal with significant transitional times such as ceasing to walk, dealing with adolescence and early adulthood (189). Transitional times often highlight the sense of loss and present significant challenges to an individual's sense of identity (189). Many of these individuals also present with irritability due to frustration of trying to perform activities

of daily living. As one person with FRDA stated "Every small detail of their lives consumes more and more of the time they used to devote to work, play and other independent activity" (285). Clinicians should be highly attuned to the possibility of depression and associated mental health issues in individuals with FRDA and ensure these issues are proactively and effectively managed.

9.2.6 Future Direction of Research

Whilst it is apparent that depression and associated mental health issues may be a greater risk for individuals with FRDA it is still not clear if the greater prevalence is due to the pathology associated with FRDA, the environmental/lifestyle changes imposed by the presence of the condition or a combination of the two. Further research is required to understand the mechanism associated with mental health issues in individuals with FRDA. Further research is also required to identify significant periods during the disease process when an individual may be at greater risk and therefore requiring prophylactic intervention including, but not confined to, intense and targeted counseling.

9.2.6 Recommendations

Recommendations	Grading
Individuals with FRDA require regular evaluation in terms of risks for developing depression and/or other mental health issues.	GPP
Individuals with FRDA may benefit from regular counseling to assist in adjusting to transitional events and possibly prevent the emergence of related depression.	GPP
Individuals with FRDA identified with depression should be treated with established interventions including counseling +/- pharmacological agents.	GPP
The risk of suicide in individuals with FRDA should be considered and managed proactively	GPP

Table 15 Summary of type, number and frequency of psychiatric conditions reported in cohort of 576 individuals with FRDA (information compiled from the Collaborative Clinical Research Network in FRDA)

Condition	Number of reports	Frequency	General Population Incidence (US-population prevalence; reported www.nimh.nih.gov)
ADD/ADHD	13	2.2%	9% (13-18 year olds) 4.1% adults
Anxiety	57	10%	18.1% adults

Autism spectrum	4	<1%	1 in 110; 8 yr old children
Bipolar disorder	4	<1%	2.6% adults
Depression	153	26.6%	6.7% adults, 11.2% of 13-18 yr olds (major depressive disorder)
Schizophrenia	1	<1%	1.1% adults
Suicide (thoughts, ideation and attempts)	5	1%	3.7 percent of adults age 18 and older in the United States had thought about suicide, 1.0 percent of adults had made plans to commit suicide, and 0.5 percent of adults had attempted suicide.

9.3 Provision of Wheelchairs and seating systems

Author: Dr Louise Corben

9.3.1 Overview

As a consequence of disease progression individuals with FRDA become increasingly dependent on adaptive equipment. Symptoms including ataxia, muscle weakness, spasticity and bony changes such as scoliosis and foot deformity interfere with the ability to mobilize, attend to personal daily tasks and to stand and transfer independently, the latter of which is the most significant contributor to ongoing maintenance of independence. Given there is limited evidence regarding the provision of adaptive equipment for people with FRDA, clinical reasoning underlying provision of adaptive equipment is largely based on evidence from similar progressive, neurological conditions. It is critical however that the clinician prescribing the equipment is familiar with the particular issues related to FRDA and experienced in the adaptive equipment prescribed. In particular the prescription of the first wheelchair can be seen as a significant milestone in the progression of the condition hence ensuring active involvement of both the client (and parents if appropriate) is both critical and essential (552).

9.3.2 Provision of manual wheelchairs and seating systems

9.3.2.1 Review of literature related to Friedreich ataxia

There is only one published study that specifically examined the prescription of wheelchairs for people with FRDA (552). This prospective two-year randomized crossover study examined 19 male participants, four of whom had been diagnosed with FRDA, although the method of diagnosis was not reported (the study predated genetic diagnosis). This study examined the efficacy of provision of a customized wheelchair seating system on sitting posture, respiration and upper limb function. While having some methodological short comings this study is important in highlighting how critical adaptive seating is to an improved seated posture. There was however little immediate effect on respiratory function and only small differences in upper limb function. An important conclusion from this study was the potential to over-correct musculo-skeletal changes and moreover in the process of correction for deformity, to further compromise functional capacity. Findings from this study reinforced that in prescribing a manual wheelchair and seating system, it is essential that functional capacity is not impeded for the sake of an anatomically correct seated posture (552, 553).

9.3.2.2 Review of literature from like conditions

As with FRDA there are few documented studies evaluating the efficacy of wheelchair and customized seating in people with like chronic neurological conditions. There are however, retrospective audits (554), review articles (221, 555) and clinical guidelines (556). People with FRDA usually present with some degree of scoliosis with associated hypertrophy of back musculature, and pelvic asymmetry. Uncorrected, this can lead to further loss of function, pain, pressure areas and compromised respiratory function (557, 558). Provision of an adjustable contoured seat that has the flexibility to correct pelvic asymmetry by the use of gel or foam inserts can be effective in preventing further deformity (556, 557, 559). Moreover the use of a contoured padded back support with either or both pelvic and thoracic lateral supports can assist in providing support in a coronal plane (558, 560). Holmes and colleagues (558) identified the efficacy of using four adjustable lateral pads in managing scoliosis related to cerebral palsy (CP). Whilst the mechanisms of scoliosis in people with FRDA have some differences to those with CP, the intervention may prove just as effective. A correctly positioned four point lap belt can maintain the person in an optimum position despite a tendency to change position as a response to coughing/laughing or sneezing.

Consideration should be given to the most appropriate type of wheelchair frame (221). Whilst people with FRDA benefit from a light weight, responsive model (often with a rigid frame) it is essential it has the strength to manage at times poorly controlled, forceful movement (221, 561, 562). Removable footplates are critical to ensure an optimum sit to stand stance during a standing transfer. Likewise the use of one-piece lift off footplates may prove easier to remove and replace as well as achieving optimum positioning for hips/knees and feet.

9.3.2.3 Provision of powered wheelchairs and scooters

Individuals with FRDA may benefit from provision of either a powered wheelchair or scooter. This equipment is particular important in facilitating community access for those who find it difficult to wheel distances in a manual wheelchair (563). As discussed previously, careful attention needs to be made to appropriate seating in addition to the programming, control, stability and storage of the chair and the mode of transfer on and off the chair or scooter (554).

With either manual or powered wheelchair it is critical that structured training programs are conducted to ensure the wheelchair user is safe, competent and confident to use the wheelchair (564).

9.3.2.4 Provision of other adaptive equipment

Individuals with FRDA benefit from the provision of grab rails to assist in attending to activities of daily living. It should be noted that given ataxia is a core element of impairment it is essential that grab rails are positioned to ensure that during the

transfer the person is able to maintain their center of gravity over their knees and feet. As such, grab rails positioned to facilitate pulling up, rather than pushing up may be of more benefit.

Likewise provision of wheeled commode/shower chairs requires customization to the specific requirements of a person with FRDA including stability and ease of maneuverability and transfer. This may include lowering the seat height to facilitate safe transfers, utilizing smaller seat apertures and ensuring an appropriate seat width to avoid extraneous trunk movement while in use.

9.3.2.5 Pediatric vs Adult individuals with Friedreich ataxia

It should be noted that the prescription of wheelchairs for children with FRDA raises different issues than those for adults with FRDA. An earlier age of onset is associated with faster rate of progression to wheelchair use (99, 565). In addition, the repeat size on GAA1 has been associated with the presence of scoliosis, wheelchair dependence, impaired vibration sense and presence of foot deformity (57). The earlier scoliosis is evident the greater is the likelihood of progression and requirement for surgical intervention (557). Prophylactic management of scoliosis in children is critical even before symptoms are apparent. The goal of seating in both pediatric and adult populations, regardless of evidence of scoliosis is to maintain the spine in a balanced position in the coronal and sagittal planes over an even pelvis (557). Prescribing a wheelchair for a child has to incorporate requirements in terms of training, growth, postural stability, completion of activities of daily living and school/leisure/home access issues (555).

9.3.3 Recommendations

Recommendations	**Grading**
Prescription of a manual or powered wheelchair or scooter should be preceded by an assessment of the home/school/work and community environment the equipment will be used in.	GPP
A comprehensive prescription of a manual or powered wheelchair or scooter should be completed by a qualified clinician familiar with the specific issues related to FRDA.	GPP
A validated assessment and evaluation tool for wheelchair and seating prescription may be used to guide the process of prescription and evaluation.	GPP
In prescribing a manual wheelchair and seating system, functional capacity should not be impeded for the sake of an anatomically correct seated posture.	GPP
Appropriate training should be provided regarding the safe use of the	GPP

wheelchair or scooter in the home or community environment.	
Suitability of the seating and wheelchair system should be evaluated on an annual basis in adults and bi-annually in children.	GPP

9.4 Independence issues

Author: Dr Louise Corben

9.4.1 Overview

Like most progressive neurological conditions, the relentless nature of FRDA can have a profound impact on the capacity to participate in daily activities, be they personal, social, vocational or community focused. The overwhelming impact on independence for people with FRDA is the associated motor impairment. In particular, people with FRDA have difficulty with multi-joint movements (dysynergia), coordinating both the spatial and temporal components of movement, terminal accuracy of movement (dysmetria), terminal accuracy of movement amplitude (tremor), maintaining consistent and appropriate force, truncal balance, muscle tone imbalance, muscle weakness and fatigue. Successful completion of most activities of personal (bathing, grooming, dressing, feeding and toileting oneself), domestic (meal preparation, household tasks) and community (driving, using public transport, shopping) activities involve multi-joint movement, balance, muscle strength, endurance, intact sensation and adequate temporal and spatial control of movement. The issue of mobility, transferring and provision of gait aids has been addressed in the topic on mobility hence this section will address independence issues in general with particular reference to intervention for issues apart from mobility.

9.4.2 Description of the natural history

White and colleagues (189) explored the transitional life events in a person with FRDA indicating that identified transitions such as becoming aware of symptoms/limitations, fear of falling and moving from an ambulant to non-ambulant status were all significant events that may herald a reduction in independence. The natural progression of the capacity to mobilize in individuals with FRDA has been previously described in section 2.6. Natural history studies that include scales such the Friedreich Ataxia Rating Scale (FARS), the Functional Independence Measure (FIM) and the Modified Barthel Index (MBI) demonstrate the significant and inexorable decline in the function of people with FRDA (216, 566). Moreover, as the disease progresses, individuals with FRDA often lose functional use of their arms which in addition to reduced mobility and trunk control potentially renders them dependent on others for the most basic of self-care activities including feeding, bathing, dressing, grooming and toileting. Not surprisingly the desire to maintain independence at whatever cost is extremely significant in the life of someone with FRDA and such desire often necessitates creative and sometime unorthodox solutions to apparent impediments to independence.

9.4.3 Current investigations

Independence in people with FRDA is measured as a component of standard measures of disease severity such as the FARS, International Cooperative Ataxia Rating Scale (ICARS) and Scale for the Assessment and Rating of Ataxia (SARA). In addition the FIM and MBI are used to measure both the impact of FRDA on functional capacity and the efficacy of intervention (6, 14). In addition to standardized and formal assessments it is essential assessment is completed in the home and/or community setting of the individual with FRDA to ensure appropriate and relevant goal-setting is achieved.

9.4.4 Interventions to maintain or improve independence for people with Friedreich ataxia

Interventions aimed at maintaining or improving independence in people with FRDA can either be compensatory, that is interventions that improve function by compensating for the underlying deficit; or restorative, that is interventions that aim to facilitate restoration of function by adaptation and recovery within the neuro-musculoskeletal system (181).

1. *Compensatory techniques* include interventions such as the use of weighted and adaptive equipment such as specialized cutlery, feeding and writing implements that feature both weighted, non-slip and larger grips (567, 568) and weighting of the distal component of the limb during activity (569-572). The use of simple strategies to decompose multi-joint movements to more accurate single joint movements (181, 573), minimizing reaching movements and stabilizing proximal joints (574) have also been proposed. Practically this includes stabilizing the elbows on the table while feeding oneself, sliding the hand on the table to facilitate grasp instead of grasping in space, use of orthotics to stabilize joints (in particular the wrist), using two hands to grasp objects or using one hand to stabilize the other while manipulating an object. Training in independence tasks may also consider the significance of visuomotor or proprioceptive loss on functional capacity. People with FRDA may use vision to compensate for sensory impairment however the inherent delay in using visual feedback to correct motor performance needs to be factored initially into training and provision of equipment (e.g. programing of motorized wheelchairs).

As mentioned, a detailed assessment of functional capacity in the context of the individual's everyday environment such as home, work or community is critical to developing appropriate strategies to improve independence. The goals of intervention aimed at maximizing function in each environmental context can be incorporated into subsequent strategies and modifications to facilitate independence. Clinical reasoning is essential to avoid a prescriptive approach to the provision of adaptive equipment. For example it is of greater benefit if people with ataxia are able to pull up, rather than push

up on grab rails in order to maintain the center of gravity over their feet and thus ensure safety while transferring. Such clinical reasoning is applicable to most provision of adaptive equipment and modification of environment. Table 16 provides a summary of compensatory techniques for specific activities of daily living.

Table 16 Suggested interventions/aids to facilitate independence in daily activities

Activity	Aid/strategy to facilitate independence
Grooming	Large, weighted grips on implements; use of two hands; stabilizing elbows while performing task
Feeding	Large, weighted grips on implements; two handled mugs; modifying food (stir-fries, pasta that only require one utensil); stabilizing elbows to perform task
Bathing	Grab rails/hand held shower hose; if standing, maintain safety by leaning against wall when shutting eyes to wash hair; equipment to sit on while bathing; liquid soap; toweling robe to assist with drying
Toileting	Grab-rails (including behind toilet and drop down to side); slide bench next to toilet; double hinged toilet seat to accommodate side transfers
Dressing	Position on bed to dress lower half of body; consideration of clothes that are easy to put on and remove; consideration of wheelchair scripting if dressing self in wheelchair
Bed	Bed sticks; adjustable high-low bed with head raiser; satin sheets for ease in rolling over; positioning of grab rails on adjacent walls for safe and effective transfers; provision of king single bed as minimum size
Home access	No steps or stairs at the access points or internally; ramps at a gradient of 1:14; door openings at least 850 mm.
Bathroom design	Stepless shower-area; non-slip flooring; basin that allows wheelchair access if indicated; lever or sensor taps; angled mirror for seated user; accessible storage areas
Kitchen	Meal preparation, sink and storage area wheelchair accessible; induction cooktops; adequate bench space between refrigerator, hot plates, sink to avoid carrying items; wall oven with side opening doors; rocker action, push-pad or toggle electrical switches; non-slip mats; kitchen trolleys
Writing	Larger grips pens; sloped writing boards; computer assisted technology
General	Environment controls; keyless entries
Driving	Hand controls; wheelchair hoist

2. *Restorative techniques* include the use of relaxation and biofeedback (575-577). Specifically, relaxation techniques with EMG biofeedback has assisted in control of

upper limb and truncal ataxia during feeding and grasping activities (576) and controlling extraneous activity during activities involving flexion and extension (577). The use of motor cortical excitation has also been proposed as being potentially useful in facilitating functional capacity in tasks of daily living in similar conditions such as multiple sclerosis (578) and neurological conditions in general (579).

9.4.5 Evidence for recommendations

There are only two studies identified that specifically evaluated intervention aimed at improving independence in individuals with FRDA (6, 14). Both studies specifically examined independence in transfers and mobility following rehabilitation or surgical intervention and as such inclusion of this evidence is not applicable to this topic. No other valid evidence on intervention to improve independence for people with FRDA exists (312).

9.4.6 Recommendations

Recommendations	Grading
Individuals with FRDA may benefit from a detailed assessment identifying barriers to independence.	GPP
Compensatory or remedial intervention may improve independence in individuals with FRDA.	GPP

9.5 Advance Care Planning and End of Life

Author: Dr Claire Bates

9.5.1 Overview

This section addresses issues arising for individuals with FRDA and their caregivers as a result of the progressive and currently incurable nature of FRDA. The areas covered are:

- Advance care planning
- Palliative care and the role of specialist palliative care teams
- End of life care

FRDA is a life shortening condition for which there is currently no known cure. Harding (58) reported the average age of death from FRDA as 37 years; however recent studies have found the average age to lie in the fourth and fifth decade (580) with heart failure and arrhythmias being the most common reported cause (81, 364). Factors such as improved medical intervention and quality of life may contribute to an increased life expectancy beyond the fifth decade (580).

Individuals at the end stage of the disease process are frequently dependent in most areas of personal care and may have profound difficulty expressing themselves as well as concomitant hearing and visual impairment. They also may have difficulty eating and swallowing which could lead to secondary problems such as aspiration pneumonia. Alternatively, people with FRDA can present with a rapid deterioration in function due to heart failure and/or arrhythmia that may or may not be secondary to other medical issues. In the latter case there may be little warning that end of life is imminent. As such it is essential to ensure appropriate discussions regarding advance care planning are held in a timely manner. Moreover it is important these discussions are held at a time when the person with FRDA can engage in discussion about advance care planning and make their plans explicit. Discussing such sensitive and important issues for the first time late in the disease process, particularly when a person may have significant expressive communication impairment, is less than ideal.

9.5.2 Evidence supporting these guidelines.

A literature search using search terms 'Friedreich's ataxia' and 'advance care planning' or 'palliative' or 'end of life care' yielded no results. Likewise, replacing FRDA with 'ataxia' yielded little other than some reports around the case of Mr Leslie Burke, a UK patient with cerebellar ataxia who took legal action against the General Medical Council (the regulatory body for UK medical practitioners) in 2005 because he wanted to guarantee that doctors would not be allowed to withdraw artificial nutrition or hydration against his wishes in the final stages of his disease. He lost his case in the court of appeal but his story highlights some of the challenges facing patients with

progressive neurological conditions. Like Mr Burke, individuals with FRDA have increasingly complex care needs as the disease progresses yet the disease process itself means that it is possible they will lose the ability to communicate with those responsible for their care just at the time when their care becomes ethically most challenging. His case draws attention to the role of advance care planning for patients with progressive ataxias and the need for education, support and guidance for patients, caregivers and staff in this difficult area.

In the absence of direct research relating to this aspect of care for individuals with FRDA, the guidance in this section is drawn from literature pertaining to other progressive degenerative neurological conditions. Although degenerative neurological conditions vary in their presentation and life expectancy, there are parallels in symptoms and the need for services (581). Indeed, a systematic review of symptom prevalence among patients affected by advanced and progressive neurological conditions found significant commonality of symptoms between patients with motor neuron disease, multiple sclerosis, progressive supranuclear palsy, multisystem atrophy and Parkinson disease and this data correlates well with symptom prevalence and challenges faced by individuals with FRDA (582). It seems reasonable therefore to apply the evidence from the wider field of progressive neurological conditions to the FRDA population.

9.5.3 Advance care planning

Advance Care Planning (ACP) is defined as "A voluntary process of discussion and review to help an individual who has capacity to anticipate how their condition may affect them in the future and, if they wish, set on record: choices about their future care and treatment and/ or an advance decision to refuse treatment in specific circumstances, so that these can be referred to by those responsible for their care or treatment (whether professional staff or family caregivers) in the event that they lose capacity to decide once their illness progresses".

ACP may lead to formalized documents, depending on the medico-legal framework of the country concerned. In some countries (examples include UK, Australia and the United States of America) patients have the opportunity to write a formal and legally binding document that details advance care plans (UK: Advance Decision to Refuse Treatment (ADRT), Australia: Advance Care Planning (ACP) United States: Advance Care Directive or Living Will). This documents the decision to refuse a specific treatment made in advance by a person who has mental capacity to do so. This decision only comes into force should the person come to lack capacity. Other outcomes of ACP may be the appointment of a Lasting or Durable Power of Attorney.

Not all individuals with FRDA are able to engage with advance care planning. The variability of personalities and coping mechanisms means that some people will seek

out all possible information about the condition and want to know everything about their likely future. Others however, will want only the information that is required to live one day at a time and will not want to be part of discussions that focus on future deterioration and further loss of function. Some will find comfort and reassurance in being able to talk and plan ahead. Others will find attempts by professionals to engage them in these conversations unwanted and distressing.

Key principles in ACP (based on *Capacity, care planning and advance care planning in life limiting illness, A Guide for Health and Social Care Staff. UK national end of life care programme May 2011.)*

1. Effective communication, carried out with compassion and sensitivity, is fundamental to the process of providing good quality person centered care towards the end of life.
2. Care planning is the first step in making care and treatment decisions for a person with life limiting illness, irrespective of their capacity to participate or to decide.
3. A person's participation in care planning (including advance care planning) is voluntary.
4. If a person with capacity chooses not to participate in care planning, their adequately informed consent must be gained in relation to any decisions about their care or treatment that result from care planning. Only a person with capacity who chooses to do so can take part in advance care planning.
5. There is a balance between the duty of providing the information a person wants or needs to ensure their adequately informed consent and over burdening a person with too much information.
6. The care provider may respond to 'cues' which indicate a person's desire to make specific wishes or concerns known, e.g. worries about who will care for them.
7. Care and treatment decision-making by a person with life limiting illness requires that the individual has the capacity to understand, discuss options available and make decisions.
8. Where a person lacks capacity to decide, care planning must focus on determining their best interests and making decisions to protect these.
9. Any information given by an individual during any care planning discussion should be recorded and used correctly (within the legal framework of the country concerned).
10. Advance care planning is an aspect of care planning which can only be undertaken by a person who has capacity to decide. No pressure should be brought to bear by a health or social care worker, family or any organization on the individual concerned to take part in advance care planning.

11. Should an individual with capacity wish to record choices about their care and treatment, or an advance decision to refuse treatment, in advance of losing capacity, they should be guided by a professional with appropriate knowledge and this should be documented according to the legal requirements of the country concerned.
12. Any choices or advance decisions to refuse treatment recorded in advance of loss of capacity only become relevant when a person loses the capacity to decide about those issues.
13. Where an individual has capacity to decide, they must check and agree the content of any care planning record.
14. Staff should make or share records of any discussion only with the person's permission or if, in the case of someone who lacks capacity, this is judged to be in their best interests.
15. There should be locally agreed policies about where care planning documentation (including any formalized outcomes of advance care planning) is kept and systems in place to enable sharing between the health and social care professionals involved in the care of the individual, including out of hours providers and ambulance services.

The person concerned should be encouraged to regularly review any care planning documentation, to update this as appropriate, and to ensure that revisions are shared with those they wish to involve in their care.

9.5.4 Recommendation

Recommendations	Grading
Professionals should facilitate advance care planning and documentation of advance care directives in individuals with FRDA.	GPP
Advance care directives documented for individuals with FRDA should be regularly reviewed by the individual in conjunction with their treating clinicians.	GPP

9.6 Palliative care

Author: Dr Claire Bates

9.6.1 Overview

"Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. Palliative care:

- provides relief from pain and other distressing symptoms;
- affirms life and regards dying as a normal process;
- intends neither to hasten or postpone death;
- integrates the psychological and spiritual aspects of patient care;
- offers a support system to help patients live as actively as possible until death;
- offers a support system to help the family cope during the patient's illness and in their own bereavement;
- uses a team approach to address the needs of patients and their families, including bereavement counseling, if indicated;
- will enhance quality of life, and may also positively influence the course of illness;
- is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life."

(WHO definition 1998)

Palliative care has historically been associated with cancer care but the expectancy and demand for palliative care provision beyond cancer has been growing in the western world in recent years. The importance of palliative care for patients with progressive neurological disease was highlighted in the UK National Service Framework for Long Term Neurological Conditions (NSFLTNC) (583). It is estimated in the UK (where specialist palliative care is well established as a specialty) that 300,000 people living with neurological conditions do not receive the specialist palliative care input that they need (584). This area is complex and detailed discussion is beyond the remit of this document, but the NSFLTNC promotes the need for coordination between neurologists, rehabilitation specialists and palliative care services in order to ensure patients receive the best possible care. Royal College Guidelines were written to support the quality requirements in the NSFLTNC. This guidance is highly relevant to individuals with FRDA, especially regarding referral criteria to palliative care services.

Experts concerned with the interface between neurology, rehabilitation and palliative care have decided to promote the concept of Neuropalliative Rehabilitation. This

involves a holistic approach to the care of neurological patients with significant disability, complex needs and a potentially shortened life span. It is patient centered and involves diagnosis of clinical problems at all stages, rehabilitation to maintain function, care coordination and when appropriate, palliation to relieve symptoms. While the provision of these three services varies from country to country and even within countries, there can be no doubt that improving the quality of life for individuals with FRDA and their caregivers will involve partnership between different specialists. As the WHO definition highlights, palliative care is not just for the end of life and many people with complex symptoms or other needs arising from FRDA will benefit from early referral to multidisciplinary palliative care teams.

9.6.2 End of Life Care

Unlike some of the rapidly fatal progressive neurological conditions, FRDA often has a disease course spanning several decades. It is often hard to know when the end of life is approaching. In other conditions, identifying the patient's last year of life is important in order to begin advance care planning. However, in FRDA, it may be necessary to engage in advance care planning some time before the individual is in the last year of life; before poor quality speech and other communication barriers intervene. Whether or not ACP has taken place before, identifying the end stage of the illness is still essential to ensure individuals and their families are provided with the most appropriate support.

Accurately predicting prognosis is virtually impossible in most advanced diseases, so clinicians can use certain triggers to identify a person approaching the end of life. One such trigger is the 'surprise question': "Would you be surprised if this patient died in the next 12 months?" (EOLC strategy 2008 prognostic indicator guidance). It should be noted however that if possible, discussions regarding end of life care should occur well before the end of life stage to ensure in the person concerned is able to communicate their desires effectively.

In addition to the intuitive surprise question, clinicians should consider general and specific clinical prognostic indicators in FRDA:

General indicators (common across different diseases):

- Progressive physical decline.
- Increasing need for support.
- Progressive weight loss.
- Repeated/ unplanned crisis admissions.

Indicators specific to FRDA:

- Complex symptoms which are too difficult to control.
- Swallowing problems (e.g. choking with meals) leading to recurrent aspiration pneumonia, sepsis, breathlessness or respiratory failure.

- Speech problems; increasing difficulty in communication plus progressive dysphasia, dysarthria and fatigue.
- Congestive heart failure indicated by the New York Heart Association classification class 3 or 4 (shortness of breath on minimal exertion or at rest).
- Voluntary cessation of essential medication, in particular related to maintaining cardiac function.

Answering 'no' to the surprise question and identifying general or disease specific clinical indicators of decline should alert the multi-disciplinary team that an individual with FRDA is approaching the end of life.

Many people do not want to talk about death and dying. Many professionals, caregivers and patients living with FRDA feel that 'staying positive' precludes discussion about end of life issues. However, to ensure individuals with FRDA receive the best possible care at the end of their lives, attention needs to be given to these issues earlier on to enable planning and preparation wherever possible. In recent years the concept of a 'good death' has emerged (585). A 'good death' usually means:

- Being treated as an individual, with dignity and respect;
- Being without pain and other symptoms;
- Being in familiar surroundings; and
- Being in the company of close family and/or friends.

Provision of high quality end of life care includes attention to the patient's preferred place of care (home, hospital or hospice) and the provision of spiritual and pastoral support. As the person enters the dying phase, the focus of treatment shifts and symptom control and comfort take precedence over life prolonging treatment such as enteral feeding. The use of validated tools such as the Liverpool Care Pathway are recommended to support staff in deciding which medication and interventions should be stopped and which should continue (586).

9.6.3 Recommendations

Recommendations	Grading
Neurology, rehabilitation and palliative care services should develop closely coordinated working links to support people with FRDA from diagnosis to death, including: • proper flow of communication and information for patients and their families • A designated point of contact for each stage in the pathway.	GPP
Individuals with FRDA and a limited lifespan (for example, likely	GPP

to die within 12 months) and/or distressing symptoms, and/or a need for end-of-life planning generally benefit from a referral to a palliative care team.	
An individual identified as dying from FRDA may benefit from ongoing access to palliative care services including symptom and pain control, psychological and spiritual support and specialist input if needed.	GPP

9.7 Potential medications/compounds for use in Friedreich ataxia

Author: Dr Caterina Mariotti

9.7.1 Overview

During the past 20 years, many potential medications have been proposed for the treatment of FRDA, and a number of pharmacological clinical trials have been conducted to explore different strategies aimed at ameliorating or preventing cell damage due to reduced frataxin.

The involvement of mitochondrial respiratory chain and oxidative stress in the pathogenesis of the disease firstly suggested the use of medications with antioxidant properties, including Vitamin E, Coenzyme Q10 and Idebenone (see Table 13). In addition, the observation of iron overload in mitochondria led to the study of iron chelators, such as Deferiprone, in clinical trials.

More recently, compounds increasing frataxin protein or enhancing frataxin gene transcription has been developed and tested in a series of pilot trials. So far, there are no proven disease-modifying treatments. Several pharmacological studies are still on-going and definite results are expected in the near future (see Table 18).

9.7.2 Drugs/Compounds under investigation that are available or approved for another indication and therefore available off-label

Idebenone

Idebenone is a short-chain benzoquinone with potent anti-oxidant properties, structurally related to Coenzyme Q10. The compound was originally developed by Takeda Pharmaceuticals Company Ltd. (Takeda) for the treatment of patients with cognitive disorders and Alzheimer disease and was approved in Japan in 1986 for the treatment of cerebral ischemia-induced lesions (587). Idebenone has been shown to inhibit lipid peroxidation, to stimulate mitochondrial functions and to improve the myocardial energy state in cardiac hypertrophy (588, 589).

In 1999, Rustin and colleagues (590), showed that Idebenone could have a protective effect on the damage to mitochondrial respiratory chain complexes jeopardized by mitochondrial iron accumulation in cells of individuals with FRDA. In the following years, the clinical safety and tolerability of Idebenone was tested in several phase 1 to phase 3 clinical trials (Table 13). Treatment was generally well tolerated, and no serious side effects have been reported even at the highest dose of 2250 mg per day (53, 54). The most commonly reported adverse events were gastrointestinal effects, such as diarrhea, nausea, and dyspepsia of mild severity. Design, time of duration, and treatment dosage has been highly variable, as well as efficacy and outcome measures regarding the

cardiac and neurological aspects of the disease. Early clinical studies, at a dose of 5 mg/kg/day, mainly reported benefits of Idebenone in FRDA-associated cardiomyopathy, without demonstrating neurological benefit.

More recent trials suggested mild improvement in neurological scores with high dose Idebenone treatment (up to 45 mg/kg/day) (53). Unfortunately, however, the clinical data from the latest phase-III studies did not confirmed the efficacy of Idebenone for the treatment of both neurological symptoms and cardiomyopathy in FRDA (54, 591{Richardson, 2013 #2779)}. As a consequence of the promising results from the first clinical studies and on the basis of the safety of the treatment, Idebenone has been used by many individuals with FRDA. The results of the latest studies did not confirm the efficacy of Idebenone on neurological symptoms, and it is still unclear whether Idebenone has cardiac benefit (Level of evidence II, Grading of recommendation B).

Deferiprone

Deferiprone, (Ferriprox®, Apopharma, Canada) is an oral iron chelator, commercially available in many countries for the treatment of iron overload in patients with thalassemia major. Redistribution of iron has been proposed as a therapeutic strategy for FRDA. In 2007, Boddaert and colleagues (592), conducted a pilot study of Deferiprone in 15 individuals with FRDA. After six months of treatment the participants had a few clinical benefits, such as improvement in manipulative dexterity and speech fluency. Subjects were treated with 20-30mg/kg/d Deferiprone. Four subjects were withdrawn due to side effects and nine completed the study. One of the four subjects had agranulocytosis and the others experienced musculo-skeletal pain, dizziness and Guillain-Barre syndrome which resolved after discontinuation of Deferiprone.

After this first study, a large multicenter double blind placebo controlled trial (sponsored by Apopharma) has been conducted in 72 individuals with FRDA aged 7 to 35 years. The participants assigned to the high-dose arm (60 mg/Kg) were prematurely discontinued due to adverse neurological events (worsening of ataxia). Other drug related side effects were iron-deficient anemia and agranulocytosis (4th International FA Symposium in Strasbourg, France 2011). In this study there was significantly greater decline in FARS score in the intermediate dose group (45 mg/Kg) compared to those on placebo. Conversely, there was a non-statistically significant reduction in left ventricular mass in those treated with Deferiprone compared to placebo.

Another open-label study was conducted in 20 individuals with FRDA, ages 8-25, for 11 months to assess combined therapy of Idebenone and Deferiprone. No significant differences were observed in total ICARS comparing baseline to the end of the study. Echocardiographic measures showed a significant reduction of left ventricular and intra-ventricular wall thickness, and magnetic resonance imaging showed a statistically significant reduction in iron in the dentate nuclei (593).

Erythropoietin (EPO)

Erythropoietin is a glycoprotein, which stimulates red blood cell production. It is produced in the kidney and stimulates the division and differentiation of committed erythroid progenitors in the bone marrow. EPO (Epoetin alfa), a 165 amino acid glycoprotein manufactured by recombinant DNA technology, has the same biological effects as endogenous erythropoietin.

Endogenous production of Erythropoietin is normally regulated by the level of tissue oxygenation. Hypoxia and anemia generally increase the production of Erythropoietin, which in turn stimulates erythropoiesis. EPO has been shown to stimulate erythropoiesis in anemic patients with chronic renal failure or with cancer.

RhuEPO has been shown to have neuro- and cardioprotective properties. Sturm and colleagues (594) suggested the therapeutic potential of rhu-EPO by demonstrating that it increased frataxin levels in cells from individuals with FRDA. The first rhuEPO pilot-study was performed in 2007 by Boesch and colleagues (595). They demonstrated significant frataxin increase in peripheral lymphocytes from individuals with FRDA treated subcutaneously with rhuEPO 5,000IU thrice weekly, for 8 weeks. Subsequently, the same individuals participated in an open-label 6-month extension study with 2,000IU rhuEPO (thrice weekly). There was a 24% increase in frataxin levels, and a statistically significant improvement in the SARA scale (56). However, safety concerns arose for those participants, with 4/8 having increased hematocrit (Hct) requiring phlebotomies. Saccà and colleagues (596) reported a statistically significant 35% increase of frataxin at 3 months after a single epoetin-alfa dose of 600 IU/Kg (max 40,000 IU). In this open-label study, the 10 enrolled subjects received two subcutaneous epoetin-alfa doses (600 and 1200 IU/kg) with a 3-month-washout interval between the two doses. Six-months after the second epoetin injection, the authors described an additional significant increase in frataxin up to 54% (596). In a more recent study, escalating rhuEPO single doses (5000, 10000, and 30000 IU) were administrated at monthly intervals. This schedule was associated with a non-significant short-term frataxin change, after rhuEPO single-dose application, but with a long-term cumulative significant frataxin increase after three months (597).

In contrast with these results, it has been recently demonstrated in a six-month, randomized placebo-controlled trial in 16 adults with FRDA treated with EPO intravenously (20,000 IU every 3 weeks; 40,000 IU every 3 weeks; 40,000 IU every 2 weeks), that EPO was safe and well tolerated, but did not result in any significant hematological, clinical, or biochemical effects in individuals with FRDA (598).

EGb-761

EGb 761 is an extract of Ginkgo biloba leaves (EGb 761®, Tanaken, Ipsen, France, http://www.ipsen.com/en/rd-primary-care). EGb 761® is indicated and registered in many countries for the treatment of cognitive disorders in the elderly and for

neurosensory disorders, such as vertigo, tinnitus, hearing loss, and retinal disorders. This compound has antioxidant and neuroprotective properties as well as an action on β-amyloid protein in experimental models.

Ipsen is conducting a clinical trial of EGb761 in France – "A Phase II, Randomised, Double Blind Study Assessing the Efficacy of EGb761 120mg Bid Versus Placebo in Patients Suffering From Friedreich Ataxia". They are recruiting individuals with FRDA between the ages of 12 - 22 years and who are ambulatory. This proof of concept study is evaluating the effect of EGb 761® on muscle energy function and mitochondrial activity by MRI spectroscopy. Results have not yet been published. http://clinicaltrials.gov/ct2/show/NCT00824512?term=egb761&rank=3

Pioglitazone

Pioglitazone hydrochloride (ACTOS®, Takeda Pharmaceuticals) is a thiazolidinedione antidiabetic agent that depends on the presence of insulin for its mechanism of action. Pioglitazone decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Unlike sulfonylureas, pioglitazone is not an insulin secretagogue. Pioglitazone is a potent agonist of peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism. However, pioglitazone and other similar medications for diabetes may cause or worsen congestive heart failure, so particular care and adequate monitoring of heart function is required during treatment. Individuals with type I diabetes and those at risk for congestive heart failure should not take pioglitazone.

Rustin has proposed investigation of pioglitazone, as a potential treatment for FRDA because it may induce the expression of many enzymes involved in mitochondrial metabolism, including the superoxide dismutases. This agent may be therapeutic by counteracting the disabled recruitment of antioxidant enzymes in individuals with FRDA. Dr. Rustin has initiated a proof of concept trial in France (Hôpital Robert Debré, Paris France) to explore the effects of pioglitazone on neurological function in 40 individuals with FRDA aged less than 22 years. The trial is ongoing.

Resveratrol

Resveratrol (trans-3,5,4'-trihydroxystilbene) is an antioxidant that is commonly found in many plants, particularly in the skin of red grapes. Resveratrol has been under intense investigation as a compound that could improve mitochondrial function and some studies suggest increased longevity, lowering glucose levels and anti-cancer activity. In addition to the antioxidant properties, resveratrol has been found to increase frataxin in laboratory studies (599). An open-label, pilot study of resveratrol has been initiated to

determine whether resveratrol increases frataxin in blood cells of individuals with FRDA. The study is completed however and results are not yet published.

Varenicline

Varenicline (Chantix®) Vareniclina (Champix®, Pfizer) is an agonist of nicotine receptors and it is used to help people stop smoking. Dr. Theresa Zesiewicz of the University of South Florida noticed that ataxia and balance problems improved in patients with various types of ataxia after they started Varenicline in an attempt to quit smoking. A Phase II pilot study began in June 2009 to investigate whether Varenicline improves neurological symptoms, such as balance, coordination, and sensory perception, all of which are significantly impaired in patients with FRDA. The study was stopped in 2010 as a result of concerns regarding safety and tolerability and worsening of gait and imbalance.

9.7.3 Drugs/Compounds under investigation that are not available for other indications

OX1

Indole-3-propionic acid (IPA) also called OX1, is a naturally occurring, small molecule that has potent anti-oxidant properties that can protect against neuro-degenerative disease. In contrast to the vast majority of antioxidants, OX1 has a rare advantage in that it cannot be metabolized through a pro-oxidant pathway. For these reasons, scientists identified the potential of OX1 for treatment of FRDA. In a recent Phase 1 safety and tolerability study conducted in the Netherlands, OX1 was demonstrated to be safe and well tolerated at all dose levels tested. ViroPharma expects to initiate a phase 2 study within 12 to 18 months after completion of longer term toxicology studies. ViroPharma intends to file for Orphan Drug Designation upon review of the phase 2 proof of concept data (600).

A0001

A0001 or alpha-tocopherol quinone (Penwest-Edison *Pharmaceuticals*) is a Coenzyme Q10 analog demonstrated to improve mitochondrial function in-vitro. A0001 pharmacokinetics were studied in a single-blind, adaptive design study in 8 healthy men. In this study A0001 was well tolerated with no serious adverse events or dose-limiting toxicities (601). A Phase II study was conducted at the Children's Hospital of Philadelphia in 2010. It was a double-blind, randomized, placebo-controlled trial of 28 day duration, that included groups taking high or low dose of A0001 or placebo. The primary clinical trial outcome was the Disposition Index, a measure of diabetic tendency, from a frequently sampled intravenous glucose tolerance test. The Disposition Index was evaluated four weeks into the trial. The secondary measure was the FARS. A0001 did not alter the Disposition Index, however a dose-dependent improvement in the FARS was noted (47).

EPI-743

EPI-743 (Edison Pharmaceuticals) is an orally absorbed small molecule that readily crosses into the central nervous system. It works by targeting NADPH quinone oxidoreductase 1 (NQO1). Its mode of action is to synchronize energy generation in mitochondria with the need to counter cellular redox stress (602). EPI-743 seems to be approximately one thousand- to ten thousand-fold more potent than CoQ10 or Idebenone in protecting cells subjected to oxidative stress in patient fibroblast assays modelling the effects of mitochondrial disease. Because of EPI-743's favorable efficacy and safety profile, and in light of the predictable mortality associated with end-stage mitochondrial disease and absence of approved therapies, the United States Food and Drug Administration granted approval to use EPI-743 to treat patients with genetically confirmed mitochondrial respiratory chain disease that were considered to be within 90 days of end-of-life care. EPI-743 was administered as a dose escalation from 50 mg bid to 100 mg tid in fourteen patients, including one person with FRDA, with severe mitochondrial respiratory chain diseases (49).

Carbamylated EPO (C-EPO)

Carbamilated erythropoietin (CEPO, Lu AA24493, H. Lundbeck A/S) is a novel cytoprotective compound currently in development for acute ischemic stroke. It is chemically modified EPO by carbamylation of lysine residues and does not bind to the erythropoietin receptor and does not have hematopoietic side-effects. Despite the lack of binding to EPO receptors, CEPO retains full cytoprotective properties. Furthermore, *in vitro*, CEPO increases frataxin levels in lymphocytes from individuals with FRDA as well as from control participants. In November 2009, Lundbeck sponsored a randomized controlled trial to evaluate the safety of two week treatment (6 doses, 3 doses per week) in individuals with FRDA, and to explore efficacy by using neurological rating scales and by exploring levels of frataxin and biomarkers of oxidative stress. In this study, CEPO did not meet the key efficacy endpoints and the results did not support further development of the drug in FRDA (Lundbeck.com).

HDAC inhibitors

HDAC inhibitors are a class of compounds that interfere with histone deactylase that functions to keep DNA tightly coiled so as to silence a gene's expression. Dr. Joel Gottesfeld of The Scripps Research Institute in La Jolla, California first described the potential use of these compounds in FRDA to overcome the gene silencing effect of the GAA expansion that underlies most FRDA. RepliGen recently identified a novel class of pimelic o-aminobenzamide HDAC inhibitors that show promise in terms of metabolic stability and brain penetration (603). A phase I safety study of RG2833 was initiated in January 2012 in Italy.

9.7.4 Supplements/Nutriceuticals

Vitamin E - Coenzyme Q10

Vitamin E and Coenzyme Q10 were the first antioxidant agents tested in FRDA (Table 13). In 10 individuals with FRDA, treated with 2100 I.U. Vitamin E/day and 400 mg Coenzyme Q10/day for 6 months, there was a significant improvement in muscle energy metabolism, as measured by ^{31}P-MRS, but neurological and echocardiographic evaluation did not show any consistent benefits (117). These individuals continued the treatment over 4 years: the bioenergetic improvement was maintained during the entire period of therapy, and the changes in total International Cooperative Ataxia Rating Scale indicated in 7 cases, a mild slowing of disease progression in kinetic scores only (135). A subsequent study on 50 individuals with FRDA randomized to receive either high or low doses of combined Vitamin E and Coenzyme Q10, demonstrated no effect of the high dose regimen after 2 years treatment (48). It is important to note that prolonged Vitamin E supplementation in healthy individuals and in patients with various diseases, at doses higher than 400 IU, was not beneficial and in a few studies, was found to be associated with increased mortality (604, 605). At present, it is not possible to recommend this treatment for FRDA (Grading B).

9.7.5 Recommendations

Recommendations	Grading
As there are no proven treatments that alter natural history it is not recommended that any pharmaceutical agent be routinely prescribed to individuals with FRDA.	A (47-50)
Idebenone is the most studied pharmacological agent in FRDA. Studies to date indicate the use of Idebenone in individuals with FRDA does not result in significant changes to neurological or cardiac status over an extended period of time.	A (47, 49-56)

Table 18 Compounds used in studies comprising individuals with Friedreich ataxia.

COMPOUND	USE	N. Pts.	Dose (daily)	Trial duration months	RCT or OLT	Results	Trial name and notes	References
DRUG ACTIVITY: Antioxidants- Free-radical Scavengers And Enhancers of Mitochondrial Function								
Vitamin E and CoQ10	C	10	Vit. E 2100 IU CoQ10 400 mg	6	OLT	Improvement in energy metabolism, no neurological or echocardiographic changes		(117)
		77	Vit. E 2100 CoQ10 400	47	OLT	Mild slowing of the disease progression in 7 cases		(135)
		50	Vit. E 2100 IU or 24IU CoQ10 600 or 30 mg	24	**RCT**	No difference on disease progression between high and low doses		(48)
Idebenone	A	3	5mg/kg	4-9	OLT	Cardiac improvement		(590)
		9	360mg	1.5	**RCT**	No difference with placebo		(606)
		38	5mg/kg	6	OLT	Cardiac improvement		(51)
		9	5mg/kg	12	OLT	Improvement in ICARS score		(52)
		29	5mg/kg	12	**RCT**	Cardiac improvement		(607)
		8	5mg/kg	12	OLT	Cardiac improvement		(608)
		20	5-10mg/Kg	Several	OLT	Improvement in ICARS score		(609)
		48	5-15-45mg/Kg	6	**RCT**	Improvement in neurological scales	NICOSIA	(53)
		104	5mg/kg	6-84	OLT	Cardiac improvement		(71)

		24	5-20mg/kg	36-60	OLT	Temporary neurological improvement in children. Cardiac stability		(109)
		70	450-900mg 1350-2250mg	6	**RCT**	No changes in ICARS score	Phase III	(54)
		232	180-360mg 450-900mg 1350-2250	12	**RCT**	No changes in neurological and cardiac measures	MICONOS Phase III	Clinicaltrials.gov ID:NCT00905268
		70	450-900mg 1350-2250mg	6	**RCT**	No changes in cardiac parameters	IONIA Phase III	(610)
		68	450-900mg 1350-2250mg	12	OLT		IONA-Open Extension	(591)
EPI-743	B	14	100-30 mg	3	C	Pts with various mitochondrial disorders (1FRDA). 11 Pts. demonstrated clinical improvement		(49)
EPI-A0001	B	31	510mg/day 750 mg/day placebo	1	**RCT**	No changes in Disposition Index from the fsIVGTT. Dose-dependent neurological improvement in FARS scores.		(47)
EGb-761	A	22	240mg	3	**RCT**	Completed. No results available yet.		clinicaltrials.gov Ipsen.com
Pioglitazone	A	40	15-45mg	24	**RCT**	Ongoing. Neurological endpoint ICARS score	ACTFRIE Phase III	clinicaltrials.gov
Resveratrol	A	30	1gr 5gr	3	OLT	Ongoing		clinicaltrials.gov
DRUG ACTIVITY: Iron Chelator								

Deferiprone	A	15	20-30-80mg/Kg	6	OLT	SAE with 80mg/kg.1 pt discontinued for agranulocytosis.		(592)
		72	20-40-60 mg/Kg	6	**RCT**	High-dose arm stopped for SAE. No neurological improvement. Safety concerns		clinicaltrials.gov Apopharma
		72	20-40mg/kg	12	OLT	No data available	Open extension	Apopharma
		20	20mg/kg and Idebenone 20mg/kg	11	OLT	No neurological improvement. Reduction of hear wall thickness.		(593)
DRUG ACTIVITY: Increase of frataxin								
EPO	A	12	5000IU, thrice a week (SC)	2	OLT	27% increase in frataxin levels		(595)
		8	2000IU, thrice a week (SC)	6	OLT	Improvement in SARA score. Increased frataxin. Safety concerns		(56)
		10	2 doses:600 and 1200 IU/Kg in 3 months (SC)	6	OLT	Increased frataxin		(596)
		5	3 doses: 5000, 10000, and 30000 IU, in 3 months (SC)	3	OLT	Increased frataxin		(597)
		16	20000IU (every 3 weeks) 40000IU (every 3 weeks) 40000IU (every 2 weeks)	6	**RCT**	No beneficial effects		(598)
CEPO	B	36	325mg thrice a week (IV)	0.5	**RCT**	No beneficial effects. No increased of frataxin.		clinicaltrials.gov Lundbeck.com

RG2833 **HDAC inhibitors**	B	20	Single dose-escalating	-	OLT	Phase I study		Repligen
Neurotransmission								

Pts = patients; RCT = Randomized, placebo-controlled trial; **OLT =**open-label trial; C = compassionate use. **ICARS:** International Cooperative Ataxia Rating Scale; SARA = Scale for Assessment and Rating of Ataxia; EPO = Erythropoietin; **CEPO = carbamylated** Erythropoietin; **FARS:** Friedreich Ataxia Rating Scale; **fsIVGTT**: frequently sampled Intra Venous Glucose Tolerance Test. **IV:** Intravenous; **SC =**subcutaneous

USE:

*A: Drugs/Compounds under investigation that are available or approved for another indication and therefore available off-label;

*B: Drugs/Compounds under investigation not available or approved;

*C: Supplements/Nutriceuticals

Appendix 1 Conflict of Interest Form

FARA (USA) would like to avoid any conflicts of interest so that the process of preparing Clinical Management Guidelines is transparent. We ask that you complete this form to identify any potential conflicts of interest. This information will be strictly confidential and will not be disclosed to any third party without your consent.

I, (insert full name) ……. declare that as far as I am aware:

☐ I have no interests to declare which relate to my involvement with FARA

Or,

☐ Any potential interests related to my involvement with the FARA have been listed below.

1. **Please list any research or educational grant received or held in the last 2 years from funding bodies excluding pharmaceutical industry with relevance to the clinical management guidelines:**

2. **Please list any research, travel, educational or other grants received from pharmaceutical industry in last 2 years where funding is relevant to the clinical management guidelines? (please include amount received)**

3. **Please list any shares from companies that could benefit from the clinical management guidelines (list company names and amount of shares currently held).**

4. **Please list any consultancy or advisory board positions you may hold that are relevant to these guidelines.**

5. **Please list any editorial positions including a member of an editorial advisory board you hold that are relevant to these guidelines.**

6. **Please list any patents held or pending or royalties received from publishing that are relevant to these guidelines.**

I undertake to advise FARA (USA) in writing if a conflict or potential conflict of interest arises in the future that may impact on these guidelines.

Signature…….Date……
Name:

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Template[1] for summarising studies addressing Intervention questions

Instructions to fill the table:

- When no element can be added under one or more heading, include the mention:
  - "Not applicable" when an item is not to be informed (according to the type of study);
  - "Not described" when an item must be informed but no information is given in the publication.
- Describe all the results given in the manuscript even if those are not relevant to the study aim.
- Refer to the addendum for added results calculated or reconstructed by the reviewer.

HEADINGS	DESCRIPTION
Bibliographic citation	Use Vancouver style (Authors[2]. Title. Journal name. Publication Date; Volume (Issue):Page (Numbers) Insert the link to the publication.
Sources of funding and competing interest	Report: ➢ The source of funding cited in the paper: give name(s) of organisation or corporation. Specify if possible the source type (public research funds, NGO, government, Academic/university healthcare industry or other) ➢ Competing interests: Write "Stated" or "Not Stated" and specify if any
Setting	Number of centres, countries involved, healthcare setting, urban/rural/mixed
METHOD	
Study design (cited by author or actual)	Specify the study design: Prospective study, randomized study, cross sectional study, retrospective study, cohort study, case control study, time series, before and after studies, other. Precise if it's the design cited by author(s).
Eligibility criteria	State the inclusion and exclusion criteria cited in the paper.
Interventions	Precise details of the interventions for each group (including dose, length, regimen and timing when relevant)
Primary outcome measure	State primary outcome measure identified by author(s), usually the one used for sample size calculation
Secondary outcome measure(s)	State secondary outcome measures identified by the author(s)
Sample size	Give the number of patients needed (= the calculated before protocol) as cited (described) by the author(s) (should clearly report if it is numbers by group or not)
Randomisation method	Describe the randomisation method and the blinding method, if relevant (as cited by authors)

[1] Minimum data abstracted from a single study to allow consistent comparison across studies and to inform a group process in evidence synthesis.

[2] Limit to the first 6 authors and then add *et al.* If there is a society, it counts as an author.

HEADINGS	DESCRIPTION
RESULTS	
Numbers	Give the number of patients involved in each group as described by the author(s). Give the number of patients analysed by group as described by the author(s), in particular in the intention to treat analysis in comparative studies
Study duration	Start and end dates of the study (precise if includes follow up or not), precise inclusion and follow up periods (length rather than dates)
Patients characteristics and group comparability	Describe baseline characteristics cited in the paper (precise if it is on involved and/or analysed numbers) Highlight discrepancies between groups (i.e. involved and analysed)
Effect size – primary outcome	Summary of the primary outcome in each and between groups: effect size and its precision (mean or percentage, p value, CI: If one or another not reported precise that it is not cited)
Effect size – Secondary outcome(s)	Summary of the secondary outcome(s) in each and between groups: effect size and its precision (mean or percentage, p value, CI: If one or another not reported precise that it is not cited)
Harms (adverse events)	Define and describe observed harms per groups as reported in the paper. Precise mean(s) or percentage(s) and p value(s), if available.
CRITICAL APPRAISAL OF THE STUDY QUALITY	
Authors conclusion	Report the authors' conclusion
Results validity	Detailed comments on: ➢ External validity: setting, inclusion/exclusion criteria, interventions, etc. ➢ Internal validity: sample size (alpha and beta used for calculation), randomisation and blinding, use of inappropriate statistical analysis, group comparability at baseline, etc. General comments (including own conclusion of the reviewer if possible)
Other /Addendum Optional	Further calculations made by the reviewer (NNT, RR, OR, CI, ..)

The evidence table working group would appreciate to hear about any comments, questions; you may have on this template. Please send your feedback to the G-I-N Office:
office@g-i-n.net

Special thanks for the development of this template are addressed to:

- Najoua Mlika-Cabanne (HAS, FR), Joint speaker
- Sara Twaddle (SIGN, UK)
- Michel Laurence (HAS, FR)
- Hans de Beer (CBO, NL)
- Robin Harbour (SIGN, UK)

Appendix 3 Template for evaluating evidence (diagnostic)

Evidence tables working group

Template[1] for summarising studies addressing a Diagnostic question

Instructions to fill the table:

- When no element can be added under one or more heading, include the mention:
  - "Not applicable" when an item is not to be informed (according to the type of study);
  - "Not described" when an item must be informed but no information is given in the publication.
- Describe all the results given in the manuscript even if those are not relevant to the study aim.
- Refer to the addendum for added results calculated or reconstructed by the reviewer.

HEADINGS	DESCRIPTION
Bibliographic citation	Use Vancouver style (Authors[2]. Title. Journal name. Publication Date; Volume (Issue):Page Numbers) Insert the link to the publication.
Sources of funding and competing interest	Report: ➢ The source of funding cited in the paper: give name(s) of organisation or corporation. Specify if possible the source type (public research funds, NGO, government, Academic/university healthcare industry or other) ➢ Competing interests: Write "Stated" or "Not Stated" and specify if any
Setting	multicenter. Country(ies). Healthcare setting.
Objective(s) of the study	Report, as cited by author(s), the objective(s) of the study including both primary and secondary aims, if applicable.
Questions addressed	Mention the questions really addressed[3] (e.g. include all questions even if only one is relevant for you at the moment, do not report questions planned to be addressed but on which no results are included) in the study including the following elements: ➢ Accuracy (comparison with a reference standard test) ➢ Reproducibility ➢ Cut-off determination ➢ Comparison of two or more tests
METHODS	
Study design (cited by author or actual)	Specify the study design: Prospective study, randomized study, cross sectional study, retrospective study, cohort study, case control study, other. Precise if it's the design cited by author(s).

[1] Minimum data abstracted from a single study to allow consistent comparison across studies and to inform a group process in evidence synthesis.

[2] Limit to the first 6 authors and then add *et al.* If there is a society, it counts as an author.

[3] Report all questions really addressed in the study, even if not expected in the aim.

HEADINGS	DESCRIPTION
Reference standard test	Describe the reference standard test: ➢ What (including the provider's name if applicable), by whom and how, when ➢ Cut-offs, categories of results ➢ Blinding (investigator) to clinical information and/or to index test results, if applicable
Diagnostic test(s) evaluated	Describe the evaluated test(s): ➢ What (including the provider's name if applicable), by whom and how, when ➢ Cut-offs, categories of results ➢ Blinding (investigator) to clinical information and/or to index test results, if applicable
Time interval and treatment(s) administered between the tests	Specify if any
Investigator(s) and assessor(s) training	Report the number, training and expertise of the people executing (investigators) and reading the evaluated test(s) and the reference standard test(s) (assessors)
Study population expected	Describe the: ➢ Aimed eligibility criteria (i.e. inclusion-exclusion criteria, stage/characteristics of the disease) ➢ Prevalence estimation of the disease in the general population ➢ Previous test(s) and/or treatment(s) undertaken
RESULTS	
Numbers	Report: ➢ Number of patients needed, involved and analysed ➢ Number of patients excluded and reasons (i.e. non-interpretable test(s) results, incomplete or missing data)
Patients and disease characteristics	Describe the actual population involved in the study: ➢ Patients: gender, age, risk factors,… ➢ Disease characteristics ➢ Include the prevalence estimation of the disease in the study population
Accuracy	Give all available figures (including sub-group figures) with 95% confidence intervals when available: ➢ Sensitivity (Se) ➢ Specificity (Sp) ➢ Positive Predictive Value (PPV) ➢ Negative Predictive Value (NPV) ➢ Likelihood ratios (LR^+, LR^-) ➢ Area under the ROC curve

HEADINGS	DESCRIPTION
Reproducibility	Give all available figures with 95% confidence intervals when available: ➢ Quantitative test: o Number of repetitions of the evaluated test o Extent of values tested o Bland & Altman agreement method o Intraclass correlation coefficient ➢ Qualitative test: o Inter-rater reliability o Test-retest reliability o Correlation coefficient
Cut-Off determination	Threshold tested, if any. Precise Se and Sp values corresponding to the cut-off selected
Comparison of two or more tests	➢ Quantitative test: report the area under the ROC curve ➢ Qualitative test: report percentage comparison: IC, p values
Adverse effects	Describe adverse effects as reported in the paper, if any: from performing tests, related to participants to the tests or related to the results of the tests.
CRITICAL APPRAISAL OF THE STUDY QUALITY	
Authors conclusion	Report the authors' conclusion
Results validity	Discuss the validity of the results and potential bias present: ➢ Internal validity: study design, sample size, blinding, appropriateness of the reference standard test as a gold standard, limitations of the reference standard test (i.e. incomplete reference standard test), interpretation of the results (taking into account the study hypotheses), comment on patients lost to follow-up (if applicable), use of inappropriate statistical analysis, etc. ➢ External validity: setting, population involved, test used, etc. General comments, including own conclusion of the reviewer, if possible.
Other /Addendum Optional	Further calculations made by the reviewer

The evidence table working group would appreciate to hear about any comments, questions, you may have on this template. Please send your feedback to the G-I-N Office: office@g-i-n.net

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- Najoua Mlika-Cabanne (HAS, FR), Joint speaker
- Hans de Beer (CBO, NL)
- Rob Cook (Bazian, UK)
- Michel Laurence (HAS, FR)
- Robin Harbour (SIGN, UK)

Appendix 4 Suggested format for presentation of each topic

1. Description of the topic (i.e., description and natural history of cardiac changes associated with FRDA)

2. Description of the natural history of the disease or condition under discussion

3. Description of current investigation and current intervention/treatment options, including conservative or expectant management

4. Identify the patient population to which they apply (ie: usual vs late onset, paediatric vs adult), bearing in mind possible differences in expected outcomes for different populations.

5. Provide a statement detailing the scientific basis on which the guidelines were developed noting the strength of the evidence on which any conclusions are based.

Included in this process is:

- Review of scientific evidence of efficacy of interventions in relation to outcomes using template provided. Critical appraisal of the relevant literature will be conducted by the PICO (patient, intervention, comparison and outcome) process.
- ***Is there Level I to IV evidence in respect of each recommendation? No? Is there consensus? Yes? Develop consensus based recommendations that indicate lack of clear evidence but acknowledge consensus.***

6. Document uncertainty associated with any conclusion (uncertainty exists where the evidence on outcomes is not strong and/or clinical opinion may differ as to what outcomes may be)

7. In the case of consensus-based guidelines, acknowledge the desirability of developing evidence-based guideline.

8. In the case of non-consensus practice statements, make clear reference to each of the schools of thought.

Source: Australian Government NHMRC Clinical Management Guideline Development; National Institute of Health and Clinical Excellence (NICE)The Guidelines Manual 2009, 2012.

Appendix 5 Grading of evidence for clinical management guidelines.

Level of evidence

I Evidence obtained from a systematic review of all relevant randomised controlled trials

II Evidence obtained from at least one properly designed randomised controlled trial

III-I Evidence obtained from well-designed pseudo-randomised controlled trials (alterative allocation or some other method)

III-2 Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group

III-3 Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.

IV Evidence obtained from case series, either post-test or pre-test and post-test.

Grading of recommendations

A. Body of evidence can be trusted to guide practice: includes one or more level I studies or several level II with low risk of bias directly applied to the target population and demonstrating overall consistency of results
B. Body of evidence can be trusted to guide practice in most situations: includes one or two studies rated as II or several level III studies with low risk of bias, directly applicable to target population, and demonstrating overall consistency of results.
C. Body of evidence provides some support for recommendation(s) but care should be taken in its application: includes studies rated as III-3 with a low risk of bias or level I or II with a moderate risk of bias, some inconsistency and applicable to target population with caveats. Population studied is different from target population however clinically sensible to apply this evidence to target population.
D. Body of evidence is weak and recommendation must be applied with caution: includes level IV or level I to IV studies with high risk of bias, inconsistent evidence and not applicable to target population.

GPP. Good practice point: Recommended best practice based on clinical experience and expert opinion.

Source: Australian Government National Health and Medical Research Council (NHMRC) additional levels of evidence and grades for recommendations for developers of guidelines (2009).
https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf

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