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STATE-OF-THE-ART REVIEW

Cardiovascular Research in Friedreich Ataxia

Unmet Needs and Opportunities

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HIGHLIGHTS

- **FRDA is a progressive metabolic disease with mitochondrial dysfunction.**
- **Patients can develop a cardiomyopathy associated with heart failure and death.**
- **A single gene defect decreases expression of FXN and may be amenable to therapy.**
- **A need exists for greater basic and clinical investigations to advance therapies.**

SUMMARY

Friedreich Ataxia (FRDA) is an autosomal recessive disease in which a mitochondrial protein, frataxin, is severely decreased in its expression. In addition to progressive ataxia, patients with FRDA often develop a cardiomyopathy that can be hypertrophic. This cardiomyopathy is unlike the sarcomeric hypertrophic cardiomyopathies in that the hypertrophy is associated with massive mitochondrial proliferation within the cardiomyocyte rather than contractile protein overexpression. This is associated with atrial arrhythmias, apoptosis, and fibrosis over time, and patients often develop heart failure leading to premature death. The differences between this mitochondrial cardiomyopathy and the more common contractile protein hypertrophic cardiomyopathies can be a source of misunderstanding in the management of these patients. Although imaging studies have revealed much about the structure and function of the heart in this disease, we still lack an understanding of many important clinical and fundamental molecular events that determine outcome of the heart in FRDA. This review will describe the current basic and clinical understanding of the FRDA heart, and most importantly, identify major gaps in our knowledge that represent new directions and opportunities for research. (J Am Coll Cardiol Basic Trans Science 2022;7:1267–1283) © 2022 The Author. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Friedreich ataxia (FRDA) is a chronic disease of metabolic disruption that is most often diagnosed in childhood or adolescence. It is inexorably progressive and often ends in early adulthood with premature death from heart failure (HF) or secondary to severe neurodegeneration (**Central Illustration**). Inherited as an autosomal recessive disorder that frequently appears around the time of puberty, families learn late of this disease and subsequently may have multiple affected children. Although classified as a rare disease with a prevalence 1 in 40,000, it is the most common inherited ataxia in humans. FRDA imposes substantially greater

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

FDA = U.S. Food and Drug Administration

GAA = triplet expansion in first intron of the Friedreich ataxia gene

FRDA = Friedreich ataxia

HF = heart failure

LV = left ventricle

LVEF = left ventricular ejection fraction

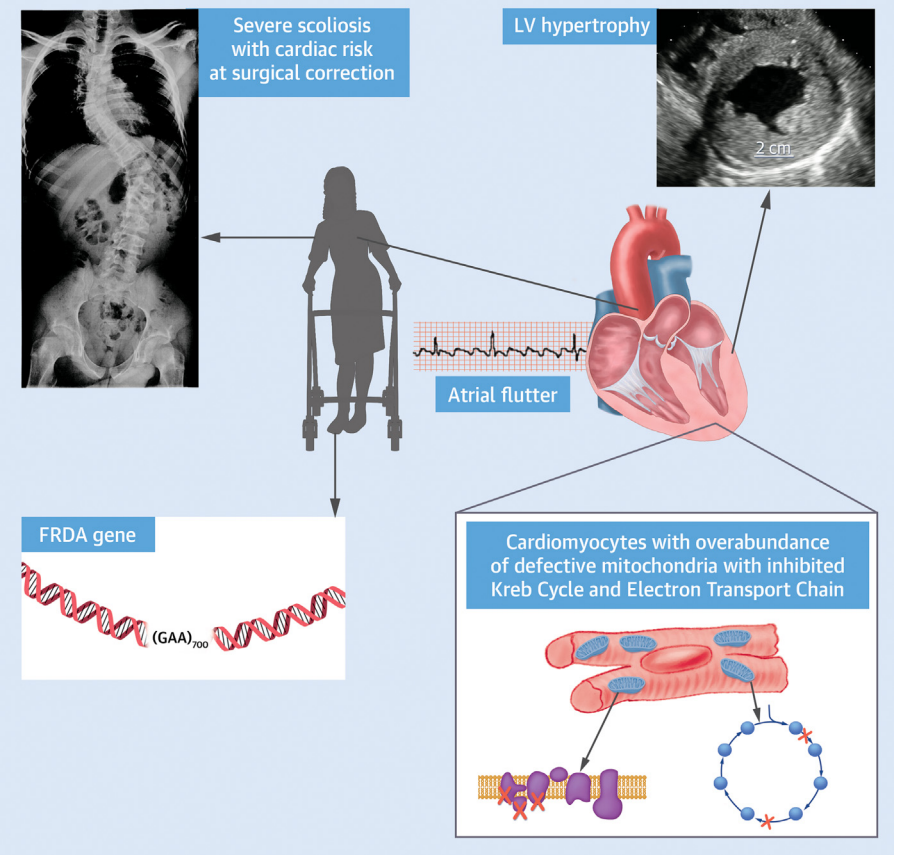
LVMI = left ventricular mass index

RV = right ventricle

burden and stress on patients and families compared with other diseases for both quality of life and expense.[1] Thus, measures that can delay the progression of cardiovascular disease, such as HF or arrhythmias, will maintain patient independence and freedom from events such as hospitalizations or emergency department visits.

The single gene defect underlying FRDA was identified in 1996 as a large triplet expansion in intron 1 of the human FRDA gene (*FXN*) (OMIM 606829) on chromosome 9q21.11.[2] This expansion silences nuclear transcription of the mitochondrial targeted protein, frataxin (FXN), and causes decreased expression of this small protein. Further studies have identified this expansion as the predominant gene defect in ~95% of cases, with ~5% of cases having a single nucleotide variation (point mutation) on one allele and an expansion on the opposite allele.[3] FXN is synthesized as a small 23 kDa precursor protein that is imported into the mitochondria where it is processed in 2 steps to a 14.2 kDa protein. It is predicted to bind iron to participate in the formation of iron-sulfur (Fe-S) clusters in the mitochondrial matrix.[4] Fe-S clusters are among the oldest conserved prosthetic groups and are found from single-celled organisms up through complex eukaryotic organisms.[5,6] FXN is also a phylogenetically ancient[7] and fundamentally important protein,[8] and it is becoming clearer just how vital it is to cellular function.[9] Multiple key enzymatic systems within mitochondria depend on Fe-S clusters for their function, such as electron transport chain complexes I, II, and III, as well as

CENTRAL ILLUSTRATION Friedreich Ataxia



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FRDA = Friedreich Ataxia; GAA = triplet expansion in first intron of the Friedreich ataxia gene; LV = left ventricle.

aconitase in the Krebs cycle. In addition, mitochondrial FXN is essential for the generation of extramitochondrial Fe-S clusters that are used in cytosolic and nuclear locations.[10,11] In the absence of or decrease in FXN expression, adenosine triphosphate production within mitochondria is severely decreased with multiple metabolic effects[12,13] and significant alterations in nuclear gene expression.[14]

CLINICAL APPEARANCE OF FRDA HEART DISEASE

As a rare genetic disease, FRDA offers a window into the fundamental biology of human development and function.[15] In this regard, the heart in FRDA is a striking example of metabolic disruption from a mitochondrial myopathy.[16] Approximately 60% of patients develop a hypertrophic cardiomyopathy that is associated with mitochondrial proliferation within the cardiomyocyte.[17,18] The severity of left ventricular (LV) hypertrophy is most often characterized as moderate to severe and concentric in nature, however, ventricular wall thickness and mass are frequently not quantified in scientific reports. The FRDA hypertrophy is typically nonobstructive, and its clinical course is in distinct contrast to the more well-recognized hypertrophic cardiomyopathy that results from defects in genes encoding the sarcomeric contractile proteins, and which frequently leads to obstruction, arrhythmias, and sudden death.[19]

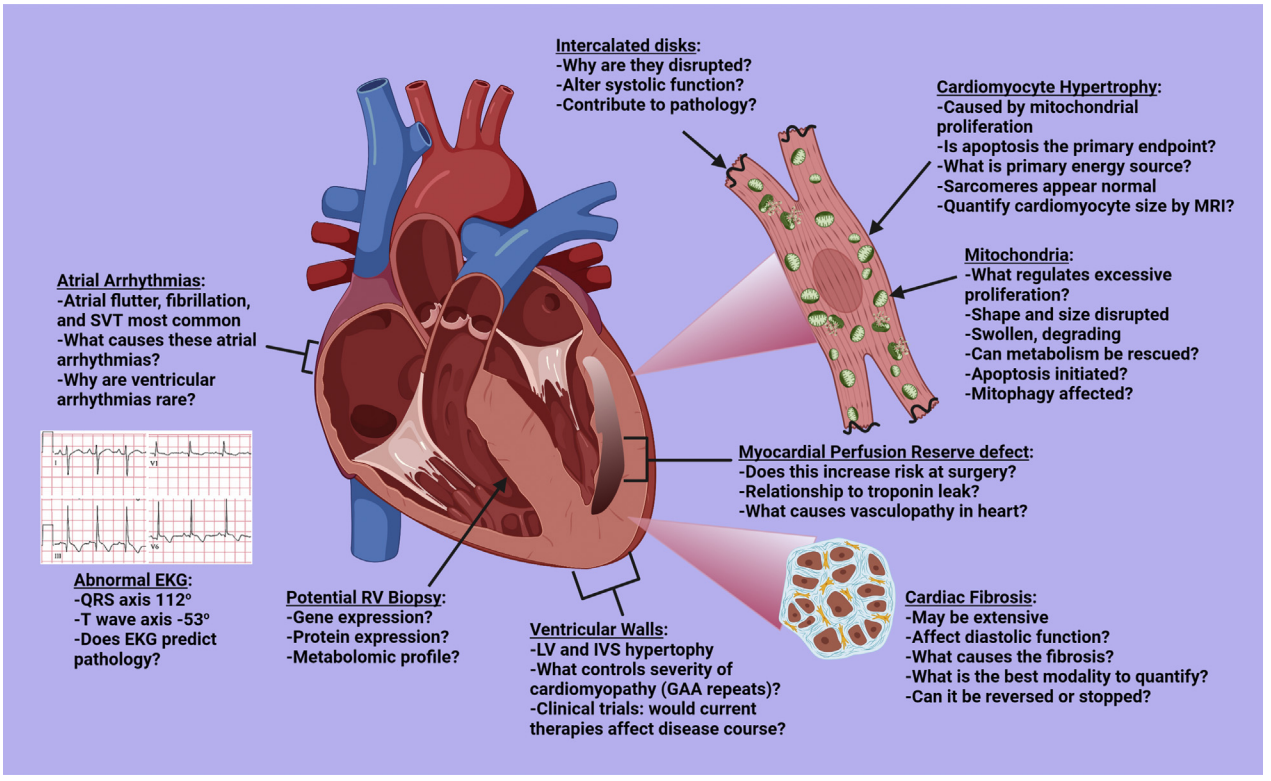
In FRDA cardiomyopathy, the mitochondria are abnormal in shape, size, and function, and animal studies have shown that the cardiomyocytes undergo chronic apoptosis.[20,21] Apoptosis in human hearts has not been reported nor investigated. This hypertrophy is associated with troponin leak in humans, suggesting ongoing injury and damage that could represent an important biomarker of disease progression.[22-24] It is unknown whether contractile protein expression and sarcomere number are affected. At both cardiac magnetic resonance (CMR) with late gadolinium enhancement and at autopsy, there can be significant cardiac fibrosis in hypertrophic hearts that may contribute to the diastolic dysfunction that has been noted in these hearts.[24-26] Missing, however, are accurate measurements of diastolic function in these patients that would allow association with outcome, especially on longer-term follow-up. Heart failure can develop in these patients with marked hypertrophy and may be associated with preserved ejection fraction.[27] In later stages of FRDA heart disease the ventricles may dilate and ejection fraction falls.[24] However, defining studies of late-stage heart disease in FRDA are lacking, which has limited our understanding and treatment of HF progression in FRDA.

Patients frequently have biochemical abnormalities that are suggestive of metabolic syndrome such as abnormal cholesterol and lipid levels and elevated hemoglobin A_{1c} levels, although they are rarely obese or hypertensive.[28] Approximately 10% of patients will develop insulin-dependent diabetes, which can have an impact on cardiac function and vascular disease in later stages.[29] Arrhythmias can become significant with advanced heart disease and are typically supraventricular in origin; for example, atrial fibrillation and flutter and supraventricular tachycardia are common and require control.[30,31] Sustained ventricular arrhythmias appear to be rare as is sudden death although further study (eg, using long-term Holter monitoring) is needed to show this.[32] Animal models of the cardiac phenotype have contributed greatly to our understanding of the basic pathophysiology and potential treatment of this heart disease.[33-36] However, these have significant shortcomings in that it is difficult to recapitulate the pathologic genotype in the mouse to allow study of the disease phenotype, especially for early developmental stages such as juvenile mice. Thus, further understanding of the human heart in this disease will require a creative integration of basic and translational technologies using human studies and animal models, as well as cell models of disease such as induced pluripotent stem cells with forced cardiac lineage. **Figure 1** summarizes many of the clinical problems and basic questions associated with the heart in FRDA.

THERAPEUTIC DEVELOPMENT IN FRDA

Logical approaches to treating heart disease in FRDA have included antioxidant treatments to mitigate free radical damage, histone deacetylase inhibitors, and iron chelation therapy to reduce iron mishandling by the cell and mitochondria.[37,38] Therapeutic trials with idebenone have shown a slight but significant decrease in LV mass over time but have shown no impact on preserving LV function.[39] Iron-chelation and free radical scavenging therapies have not shown clinical benefit and remain controversial.[40-42] β-blocking agents and afterload reducing agents have not shown significant effect on the cardiomyopathy, however, they have also not been tested in the setting of a controlled clinical trial. In particular, agents that might decrease fibrotic response, such as angiotensin II receptor blockers (eg, losartan)[43] have not been prospectively trialed. Only 1 drug, idebenone, has been prospectively trialed in children when heart disease is at an early stage and may be more

FIGURE 1 The Friedreich Heart: Basic and Clinical Questions



This figure was created with BioRender.com. CMR = cardiac magnetic resonance; ECG = electrocardiography; GAA = triplet expansion in first intron of the Friedreich ataxia gene; IVS = interventricular septum; LV = left ventricular; RV = right ventricular; SVT = supraventricular tachycardia. FRDA = Friedreich Ataxia; GAA = triplet expansion in first intron of the Friedreich ataxia gene; LV = left ventricle.

amenable to intervention. **Table 1** summarizes current novel therapeutic approaches to FRDA that have reached phase I or later in clinical trials. Supplemental Table S1 lists all therapeutic trials for FRDA as compiled from the ClinicalTrials.gov website. Of the 13 trials listed in **Table 1**, 6 of them include some measure of cardiac performance as an end point for a trial. This emphasizes the importance of understanding the cardiac clinical and basic phenotype, as well as the natural history of the heart in FRDA, which is lacking. This latter point is especially important when these novel therapeutics advance to the U.S. Food and Drug Administration (FDA) for clinical testing and approval.

CLINICAL AND TRANSLATIONAL GAPS

LONGITUDINAL STUDIES IN HEART. As a mitochondrial disease, FRDA has an impact on multiple organ systems of which the nervous system and heart are most prominently affected. Comparing these 2 systems, the appearance and progression of the neurologic findings appear to be the most consistent, thus allowing prediction of outcomes based on natural history studies.[44] A recent 5-year longitudinal study of more than 800 subjects with FRDA showed that the of the repeat size triplet expansion in first intron of the Friedreich ataxia gene (GAA) was the major determinant of neurologic progression in FRDA, and that a younger age at diagnosis also predicted faster progression.[44] This type of study where each patient has been serially evaluated at defined time points has been helpful in developing quantitative scoring systems for use in assessing patients and is of great value to the clinical trials that are currently underway.

In contrast, the heart remains relatively under studied when compared to the robust scoring systems and natural history studies for neurologic outcome despite the heart being affected in virtually all cases of FRDA.[25,45] Most of these studies have used a cross-sectional, retrospective trial design to support their

TABLE 1 Current Drugs Targeting FRDA and Engaged in Clinical Trials as of April 18, 2022

Drug	Company	Mechanism of Action	Clinical Target	Status
Omaveloxolone (RTA-408)	Reata	Nrf-2 activator. Restore mito function, reduce inflammation.	Improve neurologic symptoms and muscle strength.	Phase III trial (MOXIe trial) completed. NDA filed with FDA.
Vatiquinone (PTC-743)	PTC Therapeutics	Inhibit 15-lipoxygenase. Reduce oxidant stress and inflammation.	Change in baseline in mFARS rating scale.	Phase III trial
RT001 (dPufas)	Retrotope	Reduces lipid peroxidation from oxidant stress in mito membranes.	Cardiopulmonary exercise test.	Phase II/III trial
Nicotinamide riboside and MIB-626 (separate trials)	Children's Hospital of Philadelphia and Metro International Biotech, LLC	Increase mito NAD^+ by administering NAD precursor.	Increase exercise aerobic capacity (Vo_{2max}) and glucose homeostasis.	Phase II
Leriglitazone (MIN-102)	Minoryx Therapeutics	Selective PPAR-γ agonist. Decrease oxidant stress in mito and neuroinflammation.	Improve neurologic symptoms.	Phase II (FRAMES trial)
IMF and dimethyl fumarate (separate trials)	Ixchel Pharma and University Federico II, Naples, Italy	Increases transcription of *FXN* gene. Activates Nrf-2 activator.	1) Safety and tolerability. 2) PK/PD. 3) Improve neurologic and cardiac symptoms.	Phase I
CTI-1601 (TAT-Frataxin)	Larimar Therapeutics, Inc	Protein replacement therapy using cell penetrant peptide to deliver FXN protein.	Improve neurologic symptoms.	Phase I completed; phase II pending.
Resveratrol	Murdoch Children's Research Institute. Jupiter Neurosciences, Inc	Antioxidant, neuroprotective, decrease inflammation.	Decrease neurologic symptoms.	Phase II
Etravirine	IRCCS Eugenio Medea	A reverse transcriptase inhibitor that increases FXN levels.	1) Safety and tolerability. 2) Increasing aerobic capacity.	Phase II (Safety and Efficacy of Etravirine in Friedreich Ataxia Patients trial)
Calcitriols	Berta Alemany and Institut de Recerca Biomèdica de Lleida Fundació	Vitamin D. Increases FXN levels.	1) Safety and tolerability. 2) Change in FXN levels. 3) Activities of daily living and quality of life (neurologic function).	Phase IV (Calcitriol-FA trial)
DT-216	Design Therapeutics	Small molecule targeting the GAA repeat expansion	1) Safety and tolerability. 2) PK/PD. 3) FXN levels in blood monocytes.	Phase I (Study to Evaluate DT-216 in Adult Patients with Friedreich Ataxia)
Elamipretide	Stealth BioTherapeutics and CHOP	Mito-targeted antioxidant.	Visual acuity.	Phase I/II (ELViS-FA trial)9 Phase IA Study of AAVrh.10hFXN Gene Therapy for the Cardiomyopathy of Friedreich's Ataxia)
AAVrh.10hFXN	Weill Medical College of Cornell University and National Heart Lung and Blood Institute of National Institutes of Health.	Adeno-viral-mediated gene therapy to deliver human FXN encoding gene.	1) Safety and tolerability. 2) Change in cardiopulmonary exercise testing, cardiac arrhythmias, function, and structure.	Phase I

Data compiled from ClinicalTrials.gov and Friedreich Ataxia Research Alliance websites as of January 2022.

Calcitriol-FA = Evaluation of the Effects of Calcitriols in the Neurological Symptoms of Friedreich's Ataxia Patients; CHOP = Children's Hospital of Philadelphia; dPufas = deuterated polyunsaturated fatty acids; ELViS-FA = FRDA Investigator Initiated Study (IIS) With Elamipretide; IMF = prodrug precursor of monomethyl fumarate (MMF); IRCCS = Istituto di Ricovero e Cura a Carattere Scientifico; FDA = US Food and Drug Administration; FRAMES = Friedreich's Ataxia in Male and Female Patients; FRDA = Friedreich ataxia; mFARS = modified Friedreich Ataxia Rating Scale; mito = mitochondrial; MOXIe = RTA 408 Capsules in Patients With Friedreich's Ataxia; NAD = nicotinamide adenine dinucleotide; NDA = New Drug Application to FDA; Nrf = nuclear respiratory factor; PK/PD = pharmacokinetics/pharmacodynamics; PPAR = peroxisome proliferator-activated receptor; TAT = transactivator of transcription.

conclusions.[45-49] The number of follow-up visits and their intervals are often inconsistent, making it difficult to determine the rate of change in cardiac function. Most of these studies do not include children. Thus, the early natural history of the heart disease in FRDA is unknown. This has slowed the development of therapeutic interventions for heart in this disease, as well as limited our understanding of the basic mechanisms leading to death or morbidity in FRDA. Although the heart is cited as the primary cause of premature death in approximately 60%-80% of those patients who die with FRDA it is difficult to predict mortality or to risk-stratify outcome based on current data.[30,50]

Other investigators have also noted the significant disparity between the predictable advancement of the neurodegeneration versus the less predictable phenotype of cardiac involvement and progression.[45,51] This has made it difficult to use the cardiovascular system as an outcome measure in clinical trials, such as trials for therapeutic development. In addition, the lack of natural history studies focused

on the heart has hindered our understanding of the development of cardiovascular pathology in FRDA. Thus, neither safety studies nor therapeutic efficacy can be assessed in a clinical trial without understanding the progression of the heart disease in FRDA. This has also had a negative impact on clinical management of the heart disease in FRDA given that there is no solid data to guide treatment and evaluate outcomes. Indeed, recommendations for treatment have been based on anecdotal experience or guidelines for management of HF by the American Heart Association/American College of Cardiology, which may be unresponsive to the unique mitochondrial cardiomyopathy of FRDA.[52]

IMAGING STUDIES: ECHOCARDIOGRAPHY, CMR, AND METABOLISM. Using standard of care protocols, echocardiography has identified preliminary markers that are associated with poor outcomes in retrospective studies (see **Table 2**).[16,22,26,39,45,49-66] In a recent study examining longitudinal strain of the LV in 140 adults with FRDA (median age 34 years), 14 subjects died over 7.4 years (10% mortality rate).[49] By univariate analysis, multiple factors were associated with death including longitudinal strain, age of onset, left ventricular ejection fraction (LVEF), GAA repeat length, and LV mass. However, multivariate analysis showed that only LVEF was predictive of outcome. An earlier study from the same group had identified progressive decline of LVEF as having worse prognosis.[45] In this study, the length of the shorter GAA allele, the LVEF, and greater left ventricular mass index (LVMI) were independently predictive of mortality in multivariate analysis. Interestingly, the Kaplan-Meyer curve for this cohort showed a plateau after ~16 years of follow-up, suggesting that survivors beyond a certain point represent a subgroup that may be stable. However, the cohort numbers available for this analysis (n at each time point) decline significantly over time, indicating a larger starting cohort will be required to prove this. To date, the disparity between the cardiomyopathy progression and the neurologic impact of FRDA has not been predicted nor explained using standard of care imaging technologies, such as echocardiography or CMR.[16]

This same study found a 10-year survival rate of 88.5% that declines to ~78% by 20 years and identified 2 risk groups based on initial LVEF with differing rates of decline in LVEF: a group at low risk of death (78.6%) with stable LVEF that was normal at baseline, and a group at higher risk of death (21.4%) with lower entering LVEF that declined over time.[45] The mean age of diagnosis for FRDA was lower, the GAA repeat length higher, and the LVMI was greater for the latter group. Thus, based on these 2 studies it appears that ~80% of deaths in FRDA are attributable to cardiac causes, and 2 cardiac subgroups can be identified with differing outcomes. There is approximately a 20% all-cause mortality rate by 40 years of age, but much more work needs to be done to understand these 2 cardiac subgroups for parameters predictive of outcome, as well as to determine the cardiac mortality rate. What these and other similar studies are also missing are the early stages of disease appearance, in other words, young children. It is unknown, for example, whether the heart is hypertrophic early in life even before the appearance of neurologic findings, although 1 case report[67] suggests that it can be severely hypertrophic. Without this early natural history data, it will be difficult to understand the safety and efficacy of future therapeutic interventions for children and to justify the earliest identification of FRDA, such as during newborn screening, in a rational manner to justify starting early therapy. CMR with T_1 mapping and late gadolinium enhancement has shown an increase in the extracellular volume and cardiomyocyte size that is associated with more severe cardiomyopathy in this disease, but it has not been applied to early-stage disease where intervention might prove useful.[53] Fibrosis has also been demonstrated by CMR in those subjects with FRDA and hypertrophy.[24,26] Additionally, metabolic imaging of the FRDA heart by phosphorus P 31 magnetic resonance spectroscopy has demonstrated that energy production is abnormal.[68] Lodi et al[63] showed that cardiac creatinine phosphate/adenosine triphosphate in FRDA hearts was reduced by 40% from control subjects even in the absence of cardiac hypertrophy and dysfunction. Furthermore, myocardial perfusion reserve is compromised even in the youngest patients.[23,26]

These tools have quantified cardiac function and remodeling with a high degree of accuracy, but echocardiography is predictive of outcome in cardiomyopathies and HF only for LVEF <40%.[69,70] This is an important point to consider for FDA trial registration.[71] Relative wall thickness and longitudinal strain have also been defined in FRDA and may be useful in future studies of outcome in FRDA, but, as noted, do not predict outcome in multivariate analysis.[49,54] Other approaches, such as LVM indexed to either body surface area or height (eg, $m^{2.7}$),[72] have been predictive of outcome in hypertensive cardiomyopathy, but again these metrics have not been consistently applied or explored in FRDA. Based on data from Pousset et al,[45] LVMI may be a predictive metric in FRDA and normative values

TABLE 2 Cardiac Studies in Adults (Adults + Few Children) With FRDA After 1996

First Author	Date	Type	n	Age (y)	Major Finding(s)
Legrand, et al[49]	2021	CS	140	26-41	LVEF predicts of mortality in multivariate analysis. Longitudinal strain is not an independent predictor of mortality.
Takazaki, et al[53]	2021	CS	37	18-37	27 FRDA and 10 control subjects. FRDA CMR showed extracellular volume increased and cardiomyocyte size was larger than that of control subjects.
Peverill, et al[54]	2019	CS	216	11-46	68 children and 148 adults with FRDA. Increased LV wall thickness and smaller LV cavity associated with increased genetic severity in adults, but not in children.
Peverill et al[55]	2018	CS	132	23-41	78 FRDA and 54 control subjects. Echocardiographic analysis of RV function shows reduced systolic and diastolic RV long-axis tissue Doppler indices.
Weidemann et al[56]	2015	Long	32	20-46	Subject data compared with their echo 5 y prior in MICONOS study. Almost all FRDA with cardiomyopathy with comprehensive study. Proposed 4 progressive stages of cardiomyopathy.
Pousset et al[45]	2015	Long	133	11-62	CS 22-y follow-up of 103 FRDA survivors evaluated twice. Survival determined by cardiac complications. LVEF, LVMI, and GAA repeat best predictors of mortality.
Regner et al[57]	2012	CS	173	19.7 ± 11.6	Diastolic and systolic dysfunction and are independent. Diastolic dysfunction is the most common finding.
Friedman et al[22]	2013	CS	49	5-68	15 participants <18 y and 34 adults. Cardiac troponin I levels elevated in 47% without symptoms. ECG abnormal in 82%.
Schadt et al[58]	2012	CS	239	2-75	ECG abnormal in 90%. Neurologic score did not predict ECG.
Weidemann et al[16]	2012	CS	205	8-70	MICONOS study. Extensive evaluation. Defined 4 groups with FRDA cardiomyopathy. Neurologic scores and GAA repeat length do not predict cardiomyopathy. 68% with LVH by CMR.
Raman et al[26]	2011	CS	34	24-48	26 FRDA and 8 control subjects. MPR significantly lower in FRDA and resembles metabolic syndrome. MPR defect present without hypertrophy or HF.
Mottram et al[59]	2011	CS/long	120	22-40	60 FRDA subjects with preserved LVEF and 60 control subjects in CS study. Tissue Doppler velocities at 5 y were compared with baseline for 17 FRDA subjects. Reduction in long-axis systolic and diastolic velocities occurs well before reduction in LVEF.
Rajagopalan et al[60]	2010	CS	49	>12 to adult	CMR of 25 FRDA and 24 control subjects. LVM greater with larger GAA1 repeat number/early onset age, but longer disease duration associated with smaller LVM.
Meyer et al[61]	2007	CS	74	>16	41 FRDA and 33 control subjects. First study of CMR in FRDA. LVH in only 29%, no correlation with ataxia. ECG abnormal 89%.
Ribai et al[39]	2007	Pro/long	104	13-74	Exam every 6 mo (duration mean 5 y). 88 treated with idebenone, 16 without. Idebenone decreased LVM but function still declined. Neurologic function also declined.
Hart et al[62]	2005	CS/pro/long	77	10-57.7	77 FRDA subjects in CS and 10 in long study. All dosed with CoQ10 + vitamin E for 47 mo. Echo + cardiac ^{31}P-MRS. Improved bioenergetics by PCr/ATP ratio in heart and skeletal muscle. Heart function improved, but ataxia did not.
Lodi et al[63]	2001	CS	36	16-54	18 FRDA and 18 control subjects to measure bioenergetics by ^{31}P-MRS. LVH in 50% FRDA and normal LVEF in all. Cardiac bioenergetics reduced in all FRDA regardless of hypertrophy.
Lodi et al[64]	2001	Long	30	16-41	10 FRDA subjects treated with CoQ10 + vitamin E for 6 mo and, 20 control subjects. Heart and skeletal muscle showed sustained increase in bioenergetics by PCr/ATP ratio using ^{31}P-MRS, but no improvement in function or hypertrophy.
Dutka et al[65]	2000	CS	59	22-40	29 FRDA and 30 age-matched control subjects. Tissue Doppler-derived myocardial velocity gradient reduced in systole and early diastole in FRDA without cardiac symptoms.
Dutka et al[66]	1999	CS	55	21-39	55 FRDA subjects. Echo showed variable cardiac phenotype unrelated to ECG or neurologic phenotype.

Type indicates type of study structure: CS = cross-sectional study, Long = longitudinal.

^{31}P-MRS = phosphorus P 31 magnetic resonance spectroscopy; ATP = adenosine triphosphate; CMR = cardiac magnetic resonance; ECG = electrocardiography; FRDA = Friedreich ataxia; GAA = triplet expansion in first intron of the Friedreich ataxia gene; HF = heart failure; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; LVM = left ventricular mass; LVMI = left ventricular mass index; MICONOS = A Study of Efficacy, Safety, and Tolerability of idebenone in the Treatment of Friedreich's Ataxia (FRDA) Patients; MPR = myocardial perfusion reserve; PCr = creatinine phosphate; pro = prospective trial; RV = right ventricular.

for LVMI are available for both adults and children.[73,74] Finally, LV speckle strain has been predictive of outcome in adult-onset HF with both depressed and preserved LVEF cardiomyopathy.[75,76] Speckle tracking can detect changes in contractility before a decrease in LVEF, and there is evidence that it may be informative for outcome in the FRDA heart as well.[24,77] Thus, there is evidence that certain imaging modalities, such as strain (speckle tracking) by echocardiography or more recently myocardial fiber size by CMR[78] may provide long-term outcome prediction and/or risk stratification in FRDA. However, these technologies have not been developed and clinically deployed for FRDA in a consistent manner with long-term outcomes as a target. Indeed, almost all imaging studies have been cross-sectional in their approach.

The right ventricle (RV) remains understudied in FRDA and thus it is unknown how much RV dysfunction contributes to the long-term outcome of the heart in this disease. Palagi et al[79] studied 21 subjects who had FRDA without HF by radionuclide

angiography and compared them with 8 control subjects without FRDA. They found that 48% of subjects with FRDA had wall motion abnormalities that were most often hypokinesia of the RV anterior wall. The indices of systolic function for both RV and LV were not different from those of control subjects, although heart rates were higher in the subjects with FRDA. Weidemann et al[80] found that strain rate was decreased in the LV of subjects with FRDA, but the RV was not decreased. Peverill et al[55] examined 78 adult subjects who had FRDA without HF and 54 control subjects by transthoracic echocardiography to obtain the long-axis systolic (s′) and early diastolic (e′) peak velocities for both RV and LV. They showed that the peak velocities in the RV were lower in subjects with FRDA, indicating early impairment in long-axis function. Thus, the RV is involved early in FRDA with alterations in both function and anatomy. Because the RV is frequently difficult to image well by conventional transthoracic echocardiography in adults, superior imaging and indices of function may be better obtained with CMR and should be considered in future studies.

BIOMARKERS. Biologic biomarker analyses of blood, urine, and saliva are ongoing, and a handful of pilot studies have been published. These are needed for multiple reasons with 3 of the most prominent reasons to follow. 1) Identification of those biomarkers reflective of disease pathology that can be used as surrogate markers of outcome and for risk stratification. Because FRDA is a rare disease, this would be especially important for investigational new drug registration at the FDA or the European Medicines Agency and is an urgent need within the field of FRDA research. 2) Early identification of those patients with FRDA who are at risk for developing fatal or crippling cardiomyopathy. This would be important in management of patients undergoing stressful events, such as scoliosis surgery, in which the hypertrophic heart may be at risk. It would also identify patients needing earlier therapeutic intervention to avoid long-term complications. 3) Identification of biological markers that are reflective of the basic biochemical defect in FRDA. FRDA is fundamentally a metabolic disease and markers of the disease state that can respond rapidly are needed to support development of therapeutic interventions and inform on organ dysfunction.

In line with this, current biomarker research in FRDA was presented in depth at the 2018 Friedreich Ataxia Biomarker meeting and recently was reviewed by Blair et al.[81] Many of these studies reflect small cohorts of subjects with FRDA that have not been validated in larger studies.[82] Fibrosis of the heart is one such marker that has been studied in multiple labs. One study with 29 subjects with FRDA correlated a serum marker of collagen production, procollagen I carboxy-terminal propeptide, with CMR using late gadolinium enhancement for estimation of cardiac fibrosis.[83] They found that subjects with FRDA had significantly higher baseline procollagen I carboxy-terminal propeptide levels than control subjects did and this strongly correlated with later increases in LV end-diastolic volume. There was no correlation between procollagen I carboxy-terminal propeptide and fibrosis on late gadolinium CMR.

Use of validated, clinically available markers of cardiac injury, such as cardiac troponin I or N-terminal pro-B-type natriuretic peptide, has been sporadic and not applied as part of an organized prospective trial.[22,84] Many of the patients with FRDA chronically "leak" cardiac troponins, which is recognized in published reports about adult ischemic and cardiomyopathy as an indication of cardiomyocyte injury and death with poor long-term outcome for a variety of cardiac insults.[85-88] Although the significance of troponin leak has been underappreciated in the FRDA community, there is a growing awareness that this may be associated with cardiac hypertrophy and failure.[22] When combined with imaging studies, such as CMR or myocardial perfusion reserve studies,[26,89] cardiac troponin leak may be a sensitive indicator of ongoing cardiomyocyte injury in specific populations of FRDA cardiomyopathy (eg, the hypertrophic heart).

Finally, highly sensitive assays of FXN loss have evaluated proteomic expression and modification in FRDA. The Napierala lab[90] recently reported on the ability of a reverse phase protein array to identify protein expression profiles of primary fibroblasts from patients with FRDA, and Wang et al[91] have examined apolipoprotein A-I levels in blood as a marker of FRDA. Surprisingly, very few studies have been conducted that evaluate metabolic markers of FXN loss. For example, urinary markers of oxidant stress are predictably elevated in FRDA and appear responsive to idebenone.[92] Given that FRDA is a systemic, metabolic disease that will differentially affect all organ systems, it is logical to predict that tissues such as liver, heart, or kidney may produce biochemical markers of metabolic disruption that can be assayed in blood. HF in particular is now being investigated using metabolomic approaches to understand systemic changes with onset of cardiac dysfunction.[93] These markers may be capable of providing a rapid response to therapeutic interventions, such as histone deacetylase inhibitors, allowing dose adjustment and

TABLE 3 Cardiac Studies in Children With FRDA After 1996

First Author	Date	Type	n	Ages (y)	Major Finding(s)
Hutchens et al[23]	2021	Retro/CS	7	8-17	MPR defect present in children.
Plehn et al[100]	2018	Pro/CS	48[a]	9-17	Subclinical HCM is common. CH is associated with dysfunction.
Drinkard et al[101]	2010	Pro/inter	48[a]	9-17	Idebenone does not increase exercise capacity in FA.
Kipps et al[102]	2009	Retro/long	28	5-18	Increased LVM but stable function.
Rustin et al[103]	2002	Pro/inter	40[b]	4-22	Idebenone decreased LVM in ~50% of subjects across 6 mo.
Hausse et al[104]	2002	Pro/inter	38[b]	4-22	Idebenone decreased LVM in ~50% of subjects across 6 mo.
Rustin et al[105]	1999	Pro/inter	3	11-19	Pilot study suggests idebenone is protective in heart.
Alikasifoglu et al[106]	1999	Retro/CS	28	4-13	Cardiomyopathy in 90% of those examined by echo. Onset age correlated with cardiomyopathy.

Type indicates type of study structure. [a]Same cohort of subjects. [b]Same cohort of subjects.
CH = concentric hypertrophy; HCM = hypertrophic cardiomyopathy; inter = interventional trial; retro = retrospective study; other abbreviations as in Tables 1 and 2.

toxicity assessment more quickly than imaging technologies would allow.

CARDIOVASCULAR RISK POINTS. Clinical inflection points in the life of a patient with FRDA that represent cardiovascular risk have been very poorly studied. For example, among parent groups for FRDA, scoliosis surgery is viewed apprehensively for its perceived risk of poor cardiovascular outcome and death in their children. Over 90% of early onset (<14 years) patients with FRDA will develop significant scoliosis,[94] and a high percentage of these patients, approximately 78%, will require surgery to correct the curvature.[95,96] A very few reports have noted that surgical correction of this scoliosis carries a heightened risk of unpredictable severe HF, perioperative cardiovascular complications, and death.[95,96] There is strong rationale behind this concern for cardiac risk in surgery because the oxidative phosphorylation capacity of mitochondria in the heart is significantly decreased and the hearts are frequently severely hypertrophic.[45,63] It is unknown what the prevalence of severe hypertrophic cardiomyopathy is in cases of scoliosis requiring surgical correction.

Currently, LVEF is the most cited preoperative assessment of cardiovascular risk.[97] However, reductions in LVEF typically occur late in FRDA, making it a poor marker of cardiac disease status in these patients.[25] Given the energy requirements of the heart and the known mitochondrial dysfunction, this implies that other pathways, such as glycolysis, may serve a greater role in cardiac metabolism. Additionally, the hypertrophic heart would be predicted to be at high risk of ischemia or hypoperfusion in the subendocardium if blood pressure is lowered during surgery.[26,89] Thus, infusion of glucose in the intravenous fluids, maintenance of higher blood pressure, monitoring biomarkers of cardiac injury such as cardiac troponin I during surgery, and careful monitoring of fluid balance in the postoperative setting to avoid HF from fluid overload have been advocated by parent groups for FRDA for discussion with their surgical teams. In summary, the sensitivity of the FRDA heart to stress and fluid balance, as well as energy substrate requirements, has been understudied and would provide strong rationale for clinical advice and change in clinical practice for patients in these settings. This is especially true for the young FRDA heart.

PEDIATRIC STUDIES. For a genetic disease with its origins in the pediatric years, surprisingly little work has been done on the cardiovascular impact of FRDA in children when compared with studies in adults. As a genetic event, children are born with the gene defect responsible for FRDA. Studies have shown that loss of the *Fxn* gene in the mouse is embryonic lethal[98] and yet the human fetus with FRDA undergoes the largest rate of growth in human life in utero without apparent defect. Certainly, FRDA can and has been identified early in life and there are a few case reports illustrating early presentation of heart disease,[67,99] even before onset of neurologic findings. Yet, organized reports or studies of children <10 years of age with FRDA are rare, especially with regard to the heart.[67] This is important because there is little understanding of how the heart disease evolves during early childhood and why it might present after so many years of growth, such as in adolescence. The lack of investigation in children becomes especially urgent considering that childhood is when the greatest opportunity for therapeutic intervention may exist and where the greatest risk exists in terms of events that are stressful to cardiac function.

Since gene identification in 1996, 6 independent studies have focused on the years between childhood to young adult (see Table 3).[100-106] Only 1 longitudinal follow-up study of the heart in FRDA focused solely on children. Here, Kipps et al[102] retrospectively analyzed 28 patients with FRDA

they had followed in clinic from 1974 to 2004 at the Children's Hospital of Boston. In this study the mean age at first neurologic symptoms was 7 years and the mean age at diagnosis of FRDA was 10 years, but the mean age at first echocardiogram was 13.2 years, representing a 6-year gap until first cardiac evaluation. They concluded that patients with FRDA have increased cardiac mass but are relatively stable across childhood. The investigators did not find a correlation between either LV function or hypertrophy and the GAA repeat numbers. In a second longitudinal study that included both children and adults, Pousset et al[45] reported on a 22-year cardiac follow-up (1990-2013) of 133 patients with FRDA who were homozygous for expanded GAA repeats (see **Table 2**). Interestingly, the mean age at disease onset for these subjects was significantly older at 16 years with the mean age at first wheelchair use at 26 years. This suggests the population in the study by Pousset et al[45] was different than that in the Kipps study.[102] Cardiac hypertrophy was present in ~58% of subjects and the electrocardiogram was abnormal in 93.2%. Both studies were of cross-sectional design and retrospective and thus no information is available on changes to the individual subject's cardiac phenotype over time. This would be essential to know in a rare disease where the subject numbers are too few to define statistically relevant cohorts and the populations may differ based on multiple factors such as medical systems or genetic background. Both studies were also inconsistent in timing of follow-up visits and imaging intervals.

Three separate prospective studies on the FRDA heart in children have been published: 2 were interventional and 1 was a pilot study (**Table 3**). Both interventional trials examined the therapeutic impact of idebenone on heart and exercise. Although idebenone slightly but significantly improved LVM and systolic function,[103] it did not increase exercise capability.[101] These echographic studies in children also emphasize another key point in terms of understanding the progression of heart disease in FRDA, namely, the near complete lack in extension of new investigational techniques from adults into children. For example, there is a paucity of reports on clinical biochemistries in young children that would inform on FRDA disease early in life, such as cardiac troponins, hemoglobin A_{1c}, inflammatory markers, or lipid abnormalities. As a second example, there is only 1 report[23] extending the myocardial perfusion reserve CMR studies performed by Hutchens et al into children.[26] Further studies such as this could inform on potential risk during stressful events, such as scoliosis surgery.[95,96] Advances in understanding the fundamental biology and clinical outcomes of the gene defect in FRDA will require a greater effort to identify the heart disease as early as possible, even at birth or during fetal development,[107] such as performing fetal cardiac ultrasonography if there is a history of FRDA in the family. Thus, there is a significant need for application of new imaging and biochemical tools to the young child with FRDA. Key to this will be those multiplatform technologies that can inform on clinical phenotype using basic and translational tools that cross disciplines.

BASIC AND TRANSLATIONAL GAPS

With identification of the single gene defect in FRDA, there has predictably been a strong emphasis to develop therapeutic strategies to replace FXN using nascent therapeutic approaches before understanding what FXN actually does. Examples of this include the multiple approaches to replacing FXN protein using viral, lipid, cell-based gene therapies or protein replacement therapy. Although these efforts have progressed rapidly and are promising, they require multifactorial technologies for clinical implementation of which some are critically limiting. Mitochondria are among the most inaccessible organelles inside of the cell, and technologies to deliver a therapeutic compound into the mitochondrial matrix are young. Paradoxically, these efforts may have also diverted attention away from understanding the precise function(s) of FXN. For example, it is not known how FXN coordinates biogenesis of Fe-S clusters,[9] or whether Fe-S cluster deficiency can be mitigated within the cell and mitochondria by alternative approaches. It is also unknown and controversial whether FXN has functions in other locations within the cell, such as the nucleus or cytosol,[10,108] and it is unknown whether FXN has a biochemical activity that can be directly measured.

Relative to heart and other sarcomeric tissues, the metabolic consequences of decreased FXN are poorly explored and understood. For example, in mouse models of FRDA heart disease, there is progressive hyperacetylation of mitochondrial proteins that correlates with progressive loss of cardiac function,[12,34] but these studies have not extended to human disease. The practical question here is whether these analyses can be measured in easily obtained samples. When sampling a tissue such as blood, markers specific for heart damage are available and sensitive, but metabolic markers that may respond rapidly to a therapy or change in disease state are currently not known for FRDA. Such markers may also be reflective

of the systemic metabolic impact of FXN loss and not just the heart or development of HF.[93] A biologic marker reflecting the metabolism of FXN loss would be invaluable to the development of therapeutic interventions, such as pharmaceutical companies. Thus, it is difficult to apply therapeutic approaches using current technologies and medicines without first understanding the fundamental cellular defect.

HISTOLOGY. The histopathology of the FRDA heart has been described at the light microscopy level going back as far as the 1940s.[109] In those patients who die from FRDA cardiomyopathy, it is likely that FRDA represents a disease of replacement fibrosis rather than an infiltrative disease, such as sarcoid, amyloidosis, or hemochromatosis. At the light microscope level, there is frequently extensive loss of contractile fibers with replacement by fibrosis, and large, aberrantly shaped nuclei in the remaining hypertrophied cardiomyocytes. Hewer[50] noted in 1968 that 56% of 82 FRDA autopsy cases died with HF, a figure surprisingly consistent with today's findings.[30] Of the 27 hearts he examined for pathology, all had severe interstitial fibrosis and muscle fiber hypertrophy but typically very little cellular infiltration.[110]

The histopathology of the FRDA heart is currently being detailed primarily by the Koeppen laboratory[111,112] in Albany, New York, USA. Studies from this laboratory are informative, creative, and have advanced the field. Electron microscopy shows that the cardiomyocyte hypertrophy is associated with extensive mitochondrial proliferation as is also seen in the mouse model.[17,20] There is iron deposition within the heart and an increased prevalence of cardiomyocyte apoptosis in animal models.[18,21] In this regard, it is fortunate that the pathology of the human heart disease in FRDA closely matches the phenotype of the FRDA knockout mouse.[33,34] Mitochondria within the cardiomyocytes appear abnormal with a wide variation in size, loss of cristae, enlargement, and electron dense deposits. Because mitochondrial expansion within the cardiomyocyte likely contributes to cardiomyocyte death, it is important to better understand signaling between nucleus and mitochondria that results in this expansion.

Most of the histologic studies have been of the LV free wall or interventricular septum. The RV has been understudied in this regard. Missing here also are histologic studies of the atria, which, for example, might investigate atrial fibrosis and/or atrial myopathy, that could shed light on the atrial arrhythmias that frequently affect the FRDA heart. In particular, it would be important to determine whether the atrial arrhythmias are primary to the diseased atrial myocyte or whether they represent scar formation as a result of cell death and fibrosis. Also, electrophysiology of both atrial and ventricular cardiomyocytes, which may yield new findings relative to arrhythmias in this disease, has not been performed. This may be best facilitated by using animal models (mouse) or induced human pluripotent stem cells with forced cardiomyocyte lineage.

Coronary arteriopathy has been controversial in the published reports about the FRDA heart. Certainly, patients with FRDA frequently have chest pain that is suggestive of ischemic disease, but studies of large coronary arteries have failed to demonstrate atheroma significant enough to cause ischemic chest pain.[89] An earlier and oft-quoted investigation concluded that the coronary arteries and arterioles were smaller because of the loss of cardiomyocytes,[110] but this has been vigorously challenged.[113] Multiple investigators note that whereas the coronary arteries appear grossly patent, the coronary arteries in the range of 100-300 μm in diameter are actually smaller than normal and the walls appear to have deposits of Schiff stain-positive material, suggesting an arteriopathy.[111,112] This is important because the small arteries of the heart are not passive conduits. Rather, they must be capable of responding with dilation or constriction as metabolic demands change in the myocardium. The functional consequences of this abnormally small coronary vasculature are that they may not accommodate increased demand for blood flow. This is certainly seen on functional studies, such as myocardial perfusion reserve studies, where regions of the LV wall and subendocardium demonstrate impaired perfusion reserve with stress.[26]

METABOLISM AND MOLECULAR BIOLOGY. There are no studies of gene expression profiles in the human FRDA heart. This remains a critical limitation in understanding the long-term impact of FXN loss in the heart and would be highly informative for understanding what gene programs may contribute to the pathology of heart disease in FRDA. Again, it is likely that some of these disordered gene programs will share common pathways with established HF models, such as the mouse muscle-specific ablation of the *Fxn* gene,[33,114] and may suggest new therapeutic directions. However, fresh human cardiac tissue that is adequate for study, such as by RNA-sequencing technologies, is lacking. This might be best addressed by single-cell RNA-sequencing or spatial transcriptomic technologies based on patient cardiac biopsies rather than on autopsy specimens. This area represents an urgent need that requires greater thought for how to support basic laboratories to obtain cardiac tissue samples adequate for gene expression studies.

The hypertrophic cardiomyopathy and death in FRDA do have a moderate association with the GAA triplet expansion length, although this correlation is not high enough to allow prediction of outcome in a clinical trial for a rare disease.[45,115] This GAA expansion is unstable, and changes in the length of the repeats over time have been shown by multiple labs.[116] Recently, the Napierala lab[115] demonstrated that there is tissue-specific expansion of the GAA repeat sequence. This may explain some of the disparity between the neurologic outcomes versus heart although regulation of this expansion difference is unknown. In line with these findings, the Mirkin lab[117] recently showed that the predominant repeat-mediated sequence variant in senescent cells may involve large scale deletions of the GAA repeat region as well as the flanking DNA regions. Using quiescent, nondividing yeast containing the *FXN* gene, the investigators showed that adjacent DNA may be mutated or deleted by the mismatch repair complex, causing loss of important genetic material with time.[117] If these findings are translated to human disease, it could mean that terminally differentiated cardiomyocytes have a greater burden of mismatch repair damage over time leading to HF. These findings have not been repeated in human tissues but would have important implications both for diagnosis of FRDA, because polymerase chain reaction analysis will not detect this damage, and for targeted gene therapy in the future, such as CRISPR-mediated gene repair in FRDA.

Phenotypic response of the heart has also been noted to be highly variable between individuals with similarly sized GAA expansions, even between family members with the same expansion.[16,66] Reasons behind this are not clear but it is vitally important to understand this phenomenon. One potential explanation for this variability may be that the FRDA heart is influenced by other genetic polymorphisms that have not been defined. One such polymorphism was described by Kelly et al,[118] who found that expression of the angiotensin-II type-1 receptor was increased by a polymorphism that altered the binding site for microRNA-155. This was associated with an increase in the FRDA heart LVM and an increase in the interventricular wall thickness. Sex may also play a significant role with female patients with FRDA having less severe heart disease compared with male patients with FRDA.[119] Other potential explanations for the variability in FRDA cardiac phenotype include the methylation state of DNA sequences in triplet expansion diseases, such as FRDA, which can be significantly different than in control subjects, and somatic instability of the GAA expansion over time.[116,120,121]

It is critically limiting that our understanding of the metabolism of the FRDA heart at a cellular level is incomplete. In many respects, the failing FRDA heart is the paradigm example of an engine out of fuel as a result of cumulative abnormalities in cardiac energy metabolism.[122] As noted, the FRDA heart often resembles the biochemical and tissue pathology of the heart in diabetes[111,123] or metabolic syndrome, even though the clinical metrics to diagnose this may not be met. Thus, if energy production cannot proceed efficiently via oxidation of fatty acids through the Krebs cycle and electron transport chain, the heart must function through alternate mechanisms, such as glycolysis, and will undergo long-term consequence from loss of fuel flexibility. The concept of metabolic flexibility and HF has been an exciting direction and discovery in cardiology that has not yet extended to the FRDA heart.[124,125] Loss of metabolic flexibility in HF has been quantified, for example, by positron emission tomography in type II diabetes and may be important in the FRDA heart but has not yet been investigated.[126]

As noted, mitochondria within FRDA cardiomyocytes are abnormal, but it is unknown why mitophagy programs do not remove the damaged mitochondria[127] and whether this would represent a therapeutic target either by pharmaceutical or programmed exercise approaches as demonstrated by endurance training in the KIKO mice.[128] Studies on mitophagy programs using *Caenorhabditis elegans* and *Drosophila* FRDA models suggest this may be an important pathway for extension of cells' life span.[129,130] Because mitochondrial expansion within the cardiomyocyte appears to be the predominant reason for cardiac hypertrophy in FRDA,[17,20] and most likely the cause of cardiomyocyte death, it is important to understand signaling between nucleus and mitochondria that results in this expansion. It is also unknown what minimal level of FXN is needed to restore normal function in a cardiomyocyte and how this can be measured biochemically in the intact animal (or patient). Additionally, certain proteins within mitochondria, such as dihydrolipoamide dehydrogenase, can develop "moonlighting functions" when stressed that alter their primary function.[131] For example, dihydrolipoamide dehydrogenase develops a proteolytic activity for FXN, thereby reducing its total mass within the matrix[132] when the mitochondrial matrix becomes acidified. Thus, it is an important question to determine whether the half-life of FXN is decreased in the FRDA heart.

TABLE 4 Gaps and Opportunities in FRDA Cardiac Research

Current State	Strategies	Means to Address	Outcomes
No infrastructure or network facilitating translational and clinical cardiac research or care.	Identify those centers with expertise and interest to establish network of cardiac research centers.	Leverage existing infrastructure of collaborative networks such as the Friedreich Ataxia Collaborative Clinical Research Network.	Expert network of researchers and clinicians collaborating on cardiac studies to provide resources and infrastructure supporting drug development and clinical care focused on the heart.
	Establish standards for cardiac evaluation.	Leverage other cardiac networks such as the pediatric ACTION.	
	Establish cardiac biorepository.		
	Create data and analytics infrastructure focused on heart.		
Poor understanding of the basic mechanisms and risk factors for cardiac disease in FRDA.	Study molecular mechanisms or genetic factors that determine heart health in FRDA.	Foundation and federal grant programs to leverage existing databases and biobanks.	Understand the pathophysiology of cardiac dysfunction.
	Understand metabolism of the FRDA heart.	Multiple FRDA mouse models exist and are commercially available.	Determine molecular mechanisms regulating cardiomyopathy and mitochondrial metabolism.
	Gene expression profiling and comparison to other cardiomyopathies.	Human iPSC-derived cardiomyocytes are actively banked and available.	Determine predictive biomarkers reflective of metabolic disruption.
Suboptimal ability to address clinical sequelae in patients with FRDA.	Natural history and functional outcome studies to better understand the progression of cardiac disease and clinically relevant outcomes.	Borrow from other cardiac disease clinical end points.	Clinical measures and metrics that can serve as surrogate outcomes in clinical trials.
Longitudinal studies are lacking, especially in children.		Leverage preliminary data and experience with cardiopulmonary exercise testing.	Effectively predict, prevent, and intervene to improve cardiac outcomes.
		New patient-related outcomes that capture fatigue and other patient-relevant symptoms that could be cardiac related.	
The lack of predictive cardiac biomarkers and clinical end points makes it difficult to design and implement clinical studies.	Assess biomarkers used in larger and more common cardiac diseases and trials. Can they be translated to FRDA cardiomyopathy?	Define and encourage assessment of existing cardiac biomarkers and end points in ongoing trials to establish relevance to FRDA.	Design and conduct cardiac-specific trials with relevant end points.
		Interrogate current biospecimens that are available.	Alignment of end points with regulatory authorities.
Current cardiac treatments are targeted to symptoms and are not disease-modifying.	Prospective clinical trials informed by underlying pathophysiology to test effectiveness of current palliative therapies.	Understand the patient perspective of the relevance for treating cardiac disease.	Introduce disease-modifying treatments.
		Clinical trials and therapies informed and guided by basic investigations.	

ACTION = Advanced Cardiac Therapies Improving Outcomes Network; FRDA = Friedreich ataxia; iPSC = induced pluripotent stem cell.

CONCLUSIONS

Three major factors have changed over the past 30 years that affect current interpretation of cardiac data and planning future studies in FRDA. 1) The gene defect has been identified. Polymerase chain reaction analysis now allows definitive diagnosis very early in childhood rather than waiting until symptoms, which are typically neurologic, are clear. Awareness and sensitivity to the clinical presentation of FRDA is also higher, again leading to earlier testing and diagnosis. 2) Significant advances in molecular technologies for interrogating gene expression and metabolism in heart have occurred. These techniques can allow new discovery from even small biopsies of human FRDA heart. 3) Advances in cardiac imaging technologies now allow greater insight into pathologic remodeling, metabolism, and function over time. Both echocardiography and CMR now allow unparalleled imaging and quantification of cardiac parameters. With these advances in imaging and molecular technologies, and patient registries established in multiple countries, it is reasonable to initiate prospective clinical trials to evaluate current therapeutic approaches and generate new discovery for HF in FRDA. **Table 4** contains a summary of these gap and research opportunities in FRDA research, and Supplemental Table S2 lists some of the major resources available to accelerate these investigations.

A key basic question remains for how the fetus and young child can function and grow so well with decreased expression of such an important gene. Fe-S clusters are fundamental not only for mitochondrial function but also for nuclear gene regulation.[133,134] Thus, if there is not a significant loss of FXN expression in the FRDA fetus, then what gene programs are responsible for its expression that might be taken advantage of in older patients? Conversely, if there is significant loss of FXN during embryogenesis, how does the fetus bypass the loss of Fe-S clusters, which are presumably decreased? It should be noted that both fuel substrate and oxygen tension are substantially different in the fetal environment than after birth, and these factors certainly affect mitochondrial function in the fetus. The issue of developmental progression of FRDA becomes important when trying to understand the natural history of heart disease in FRDA and determine the timing of therapeutic intervention. Important resources needed to study both basic and translational events in FRDA have been established, including human induced pluripotent stem cell banks[135] and numerous mouse models[33,128,136] (Supplemental Table S2). These resources are readily available to established and new investigators.

Finally, it is logical to assume that the disease phenotype becomes apparent when enough tissue and cellular function has been lost to overwhelm the physiologic redundancy that all vertebrate animals have in major organ systems. Any meaningful "staging" or predictive tools for outcome must include the young. Otherwise, cross-sectional studies are biased and not useful (see Peverill letter[137]). Earlier diagnosis is certain to generate a better understanding of the natural history of the heart in this disease, as well as identifying fundamental mechanisms of Fe-S cluster assembly and regulation.

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KEY WORDS cardiomyopathy, frataxin, Friedreich ataxia, heart, mitochondria

APPENDIX For supplemental tables, please see the online version of this paper.