

# Overview of Biomarkers and Clinical Assessments for FA

FARA has worked with the Friedreich's ataxia (FA) community through the years to help develop clinical outcome assessments and biomarkers for use in clinical trials. Biomarkers and clinical outcome assessments are needed for a variety of contexts of use, including diagnosis and staging of disease, patient selection for trial enrollment, proof of mechanism of a putative therapeutic, as well as evidence of efficacy needed for approval of a treatment.

The Friedreich's Ataxia Rating Scale, or FARS along with a disability rating scale, activities of daily living scale and functional measures were originally validated as part of the FA Clinical Outcome Measure Study (FACOMS). Now in use is a subscore of the FARS or the mFARS, which has been accepted as an efficacy endpoint for late-stage trials in FA and supported regulatory approval of omaveloxolone, the first approved treatment for FA. Other rating scales, functional endpoints and biomarkers have also been explored and/or used in natural history studies and in interventional trials.

To learn more about the modified Friedreich's Ataxia Rating scale view the [mFARS Info Sheet](#).

The table on the next page, last updated July 2023, gives an overview of biomarkers and clinical outcome assessments evaluated for FA clinical trials.

# Table of Clinical Tools for the Development of Therapeutics for Friedreich's Ataxia

Collated by the Friedreich's Ataxia Research Alliance | August 2023

FARA has worked with the Friedreich's ataxia (FA) community through the years to help develop endpoints and biomarkers for use in clinical trials. A need for biomarkers for various contexts of use has been recognized, and data has been collected for a variety of such markers.

Color Key	Biomarker	system	FDA Class								References	Used in a clinical trial	Useful in pediatric trials?	Notes	
			Diagnostic	Monitoring	Predictive	Prognostic	PD/Response	Safety	Endpoint	Stratification					
Validated	FXN mRNA-ddPCR	blood, fibroblasts, buccal cells						X				DT-216 NCT05285540	yes		
Utility may not be universal in all studies	Fratxin protein-mass spec assay	blood, fibroblasts, buccal cells	X	X		X	X					Guo et al. 2018b, Guo et al. 2018a; Blair et al. 2019	CTI-1601 NCT05579691	yes	
Not useful in FA	Protein expression panels	blood, fibroblasts, buccal cells			X		X					Indicato et al 2023; Napierala et al. 2021, Pathak et al. 2019	Erythropoietin (rhuEPO) NCT01016336	unknown	
	Cardio-Pulmonary Exercise testing	heart								X		Legrand et al 2022; Pane et al. 2020; Drinkard et al. 2010	Epoetin Alfa (FRIEMAX) NCT01493973; RT001 NCT 04102501; NAD+ Precursor MIB-626 NCT04817111; NAD+ and Exercise in FA (ExRx in FA) NCT04192136; GT for cardiac LX2006 NCT05445323; AAVrh.10hFXN NCT05302271; RTA 408 MOXle NCT02255435	possibly (age 10 and older)	
	Echocardiographic measures: EF, wall thickness, diastolic function, strain	heart		X		X	X	X		X		Legrand et al 2019;Pevenill et al. 2019	Etravirine (FAEST1) NCT 04273165;GT for cardiac LX2006 NCT05445323	unknown	
	Cardiac MRI: Gadolinium enhanced T1	heart		X		X				X		Takazaki et al 2021	Elamipretide (ELVIS-FA) NCT05168774; GT for cardiac LX2006 NCT05445323	unknown	
	Cardiac MRI: strain	heart		X		X				X		Legrand et al 2021	Idobenone NCT00229632; Elamipretide (ELVIS-FA) NCT05168774	age 16 and older	
	Cardiac MRI: Left ventricle mass	heart		X		X				X		Legrand et al 2020, Hutchens et al. 2021, Mahishi et al. 2012, Coelho-Filho et al 2016	Idobenone NCT00229632	unknown	
	Cardiac MRI: cardiomyocyte size (tau)	heart		X		X				X		Coelho-Filho et al 2016		unknown	
	insulin and glucose metabolism: disposition index, insulin sens., insulin secretion, glucose tolerance	metabolism		X				X				Greeley et al 2014; Azzi et al 2018	NAD+ and Exercise in FA (ExRx in FA) NCT04192136	unknown	
	Bone mineral density	metabolism		X		X			X	X		Eigentler et al 2014; Dunn et al 2022		unknown	
	OGTT	metabolism		X		X		X				Azzi et al 2019	NAD+ and Exercise in FA (ExRx in FA) NCT04192136	unknown	
	Body mass index and height	metabolism		X		X			X			Patel et al 2021; Basquez-Trincado et al. 2022	FA-COMS NCT03090789	yes	FA COMS will become part of the global UNIFA study
	FA-HI (FA Health Index, caregiver and patient versions)	N/A								X		Seabury et al 2023	Now in FA-COMS NCT03090789	yes	
	MRS imaging of brain NAA/ ml ratio (N-acetylaspartate / myoinositol ratio)	neuro						X				Gramegna et al 2017; Joers et al. 2018	MIN-102 (FRAMES) NCT03917225; TRACK-FA NCT04349514	Ongoing	
	Neuroinflammation – PET imaging	neuro				X		X				Khan et al. 2021	TRACK-FA NCT04349514	Ongoing	
	Structural MRI: spinal cord morphometry	neuro		X		X				X		Keresztes et al 2022; Selvadurra et al 2021	MIN-102 (FRAMES) NCT03917225; TRACK-FA NCT04349514	Ongoing	
	Structural MRI: brain DTI/white matter (DTI: diffusion tensor imaging)	neuro		X	X					X		Straub et al 2020; Harding et al 2021	MIN-102 (FRAMES) NCT03917225; TRACK-FA NCT04349514	Ongoing	
	mFARS (Friedreich's ataxia Rating scale)	neuro								X		Rummeley et al. 2020; Rummeley et al. 2019; Lynch et al. 2006; Subramony et al. 2005; Friedman et al. 2010; Burk et al. 2009	FA-COMS NCT03090789; FA-Children NCT03418740; RTA 408 MOXle NCT02255435; Vatiquinone MOVE-FA NCT04577352	yes, but only in >10yrs olds; specific components most useful	<a href="https://www.curefa.org/pdf/instructions-for-administering-the-mFARS.pdf">https://www.curefa.org/pdf/instructions-for-administering-the-mFARS.pdf</a> <a href="https://www.curefa.org/pdf/research/mFARS-Info-Sheet.pdf">https://www.curefa.org/pdf/research/mFARS-Info-Sheet.pdf</a>
	FARS ADL (FARS activities of daily living scale)	neuro								X		Rummeley et al 2022; Reetz et al 2016	Gamma IFN NCT0388664; Vatiquinone MOVE-FA NCT04577352; FA-COMS NCT03090789; FA Children NCT03418740	yes	<a href="https://www.curefa.org/pdf/ActivitiesOfDailyLiving.pdf">https://www.curefa.org/pdf/ActivitiesOfDailyLiving.pdf</a>
	MFIS (Modified Fatigue Impact Scale, from MSQLI)	neuro								X		Bernisson et al. 2019	A0001 alpha-tocopherolquinone NCT01035671; Vatiquinone MOVE-FA NCT04577352; RT001 NCT 04102501	unknown	<a href="https://www.commondataelements.ninds.nih.gov/report-viewer/25235/Modified%20Fatigue%20Impact%20Scale%20(MFIS)">https://www.commondataelements.ninds.nih.gov/report-viewer/25235/Modified%20Fatigue%20Impact%20Scale%20(MFIS)</a>
	25 foot walk	neuro								X		Fahey et al. 2007; Lynch et al. 2005	Calcitriol NCT04801303; Acetyl-L-Carnitine NCT01921868; EPI-743 NCT01962363; Deferiprone NCT00530127; Methylprenisolone NCT02424435	unknown	<a href="https://www.commondataelements.ninds.nih.gov/report-viewer/23535/Timed%2025-Foot%20Walk%20(T25-FW)">https://www.commondataelements.ninds.nih.gov/report-viewer/23535/Timed%2025-Foot%20Walk%20(T25-FW)</a>

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			Diagnostic	Monitoring	Predictive	Prognostic	PD/Response	Safety	Endpoint	Stratification				
	9 hole peg test	neuro							X		Lynch et al. 2006	Micronised resveratrol NCT03933163; Calcitriol NCT04801303; Defeniprone NCT00530127; Methylprenisolone NCT02424435	unknown	<a href="https://www.commondataelements.ninds.nih.gov/report-viewer/23844/Nine%20Hole%20Peg%20Test">https://www.commondataelements.ninds.nih.gov/report-viewer/23844/Nine%20Hole%20Peg%20Test</a>
	AIM-S spoon	neuro							X		Corben et al. 2021; Nguyen et al. 2020a; Nguyen et al. 2020b	Micronised resveratrol NCT03933163; FA COMS NCT03090789	unknown	link to access/purchase **ask LC
	AIM-S Cup	neuro							X		Krishna et al. 2020; Krishna et al. 2021	FA COMS NCT03090789	unknown	link to access/purchase **ask LC
	QSM Imaging of iron in dentate nucleus	neuro/metabolism		X				X			Ravanfar et al 2021; Deistung et al 2016	MIN-102 (FRAMES) NCT03917225	unknown	
	Quantitative sensory testing	neuro/sensory		X							Creigh et al. 2019		unknown	
	Meissner Corpuscle imaging	neuro/sensory		X							Creigh et al. 2019		unknown	
	OCT – Vision biomarker	neuro/vision		X	X						Rojas et al. 2020; Seyer et al. 2013; Dag et al. 2014; Fortuna et al. 2009	Elamipretide (ELVIS-FA) NCT05168774; FA COMS NCT03090789	age 16 and older	
	Redenlab speech battery	speech							X		Voget et al. 2017	RT001 (dPUFAs) NCT04102501; micronised reveratrol NCT03933163; FA COMS NCT03090789; Gamma IFN NCT01965327; Vatiquinone MOVE-FA NCT04577352	age 12 and older	<a href="https://redenlab.com/">https://redenlab.com/</a>
	Corneal nerve fiber density, or fiber length as measured by corneal confocal microscopy	vision		X							Pagovich et al. 2018		unknown	
	Low contrast visual acuity	vision							X		Hamedani et al. 2018	Elamipretide (ELVIS-FA) NCT05168774; Defeniprone NCT00530127; FA COMS NCT03090789	age 16 and older	<a href="https://commondataelements.ninds.nih.gov/report-viewer/23847/Sloan%20Low%20Contrast%20Letter%20Acuity">https://commondataelements.ninds.nih.gov/report-viewer/23847/Sloan%20Low%20Contrast%20Letter%20Acuity</a>
Utility may not be universal in all studies	frataxin protein-dipstick	blood, fibroblasts, buccal cells				X	X				Lazaropoulos et al. 2015; Deutsch et al. 2010	Gamma IFN NCT01965327	unknown	
	methylation of FXN	blood, fibroblasts, buccal cells				X	X				Rodden et al. 2022; Lam et al 2023		unknown	
	Cardiac MRI: Myocardial Perfusion Reserve	heart					X				Raman et al. 2011; Hutchens, Johnson and Payne 2021		unknown	
	Cardiac <sup>31</sup> -phosphorus ( <sup>31</sup> P) MRS PCr/ATP	heart		X			X				Loft et al. 2001, PMID 11357949	NAD+ Precursor MIB-626 NCT04817111	unknown	
	Serum markers of fibrosis (Galectin, PIIINP)	heart			X	X			X	X	Mehta et al. 2016, Legrand et al. 2020		unknown	
	EKG, Holter	heart	X						X		Weidemann et al. 2015; Mejia et al. 2021	GT for cardiac LX2006 NCT05445323	unknown	
	Serum markers of inflammation (CRP, ferritin)	heart				X	X			X	Biolotta et al. 2019		unknown	
	Cardiac MRI: Native T1	heart		X		X				X	Takazaki et al. 2021; Mavrogeni et al. 2020		unknown	
	Serum markers of myocardial damage (troponin I)	heart				X			x	X	Legrand et al. 2020, Hutchens et al. 2021, Mahishi et al. 2012	Cardiac phenotype NCT02316314	unknown	
	Serum markers of stress response (GDF15, FGF21)	heart?				X	X			X	Picca et al 2022; Pandhi et al 2022		unknown	
	Metabolic isotopologues	metabolism					X			X	Worth et al. 2015, Lynch et al. 2019		unknown	Assay and sample handling not clinical trial friendly
	Creatine chemical exchange saturation transfer MRI (CrCEST)	muscle		X			X				Schur et al. 2021, 2022; DeBrosse et al. 2016	NAD+ precursor MIB-626 NCT04817111	unknown	
	Grip strength via hand grip dynamometry	muscle		X			X					NAD+ precursor MIB-626 NCT04817111	unknown	
	Skeletal muscle transcriptomics	muscle		X			X				Indicato et al 2023	Erythropoietin (rhuEPO) NCT01016336	unknown	
	Complex I PET (positron emission tomography)	neuro or heart					X				Liu et al 2022; Schur et al 2022		unknown	
	Nrf-2 target genes	blood					X				Reisman et al 2019	RTA 408 MOXie NCT02255435	unknown	
	Ceramides	blood					X				Wang, Xu, Mesaros, 2021		unknown	
	C13 glucose metabolism in dentate(by imaging)	neuro					X						unknown	Umninn - unpublished study that demonstrated increased glucose metabolism
	SARA (Scale for assessment and rating of ataxia)	neuro								X	Burk and Sival 2018; Schwabova et al. 2014; Burk, Schulz and Schulz 2013; Marelli et al. 2012; Saute et al. 2012; Burk et al. 2009	Etravirine (FAEST1) NCT04273165; Gamma IFN NCT0388664; Calcitriol NCT04801303; MIN-102 (FRAMES) NCT03917225	unknown	<a href="http://www.ataxia-study-group.net/html/about/ataxiascales/sara/SARA.pdf">http://www.ataxia-study-group.net/html/about/ataxiascales/sara/SARA.pdf</a> Less regulatory support
	CCFS (Composite Cerebellar Functional Severity Score - combines 9 hole peg and click test)	neuro								X	Languy Melac et al. 2018; Destrebecq et al 2023	MIN-102 (FRAMES) NCT03917225		Devices are difficult to acquire; only available at several EFACTS sites. June 2023. kit available to order from INSERM - Paris
Wearable devices for ataxia	neuro								X	Muller et al 2021; Kadirvelu et al 2023		possibly	Several new/ongoing studies in progress - July 2023	
1 minute walk	neuro								X	Patel et al 2019	Methyprednisolone NCT02424435; RT001 NCT04102501 FA Children NCT03418740; MOVE-FA add NCT FA Children NCT03418740	possibly	Longer walk tests not useful due to fatigue	
Berg Balance Scale	neuro								X	Stephenson et al. 2015		possibly		
Neurofilament Light Chain in blood or CSF	neuro					X				Frempong et al. 2021, Clay et al. 2020, Hayer et al. 2020, Zeilberger et al. 2018	TRACK FA (serum) NCT04349514	unknown	Most studies have shown that NFL is elevated in children but generally decreases with age/ disease duration	

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	Brainstem auditory evoked response (BAER)	neuro		X						X	Naeije et al. 2021; Zeigeltobm et al 2018; Santoro et al. 2000, Finocchiaro et al. 1985		unknown	
	NAD+ in whole brain	neuro		X					X				unknown	
	Neuroinflammation imaging PET	neuro/heart		X		X			X				unknown	
	Skeletal muscle and brain NAD+ at 7T MRI	neuro/muscle		X					X		Bagga et al 2019	NAD+ Precursor MIB-626 NCT04817111	unknown	
	Motor evoked potential (MEP)	neuro/muscle	X	X						X	Naeije et al. 2021; Santoro et al. 2000; data presented at FARA biomarker meeting, Tampa 2018		unknown	Scoring does not have outcomes that allow for clinically meaningful interpretation
	Longitudinal gait analysis (SARA @home)	neuro/muscle		X					X		Vasco et al 2016; Summa et al 2020		unknown	Segmental analysis of ataxic gait provides sensitive measures to detect specific longitudinal and functional alterations, more than the SARA.
	Visual Functioning Questionnaire	vision		X							Alsharian et al 2020	Elamipretide (ELV-is-FA) NCT05168774	unknown	<a href="https://www.nei.nih.gov/learn-about-eye-health/outreach-resources/outreach-materials/visual-function-questionnaire-25">https://www.nei.nih.gov/learn-about-eye-health/outreach-resources/outreach-materials/visual-function-questionnaire-25</a>
	High contrast visual acuity	vision		X						X	Hamedani et al 2018	Elamipretide (ELV-is-FA) NCT05168774	unknown	
	Gene expression panels	n/a									Napierala et al. 2021; Nachun et al. 2018			Test was very long and exhausting for patients; scoring was difficult to interpret/clinical meaningfulness
	Patient Global Impression of Change	n/a												Routinely used in trials; however limited sensitivity
Not useful in FA	Serum markers of myocardial damage (galectin, other markers of fibrosis)	heart												Does not correlate with progression or symptoms of cardiomyopathy
	Metabolomic panels	metabolism									Napierala et al. 2021			
	Mitochondrial number	n/a												
	miRNA	n/a									Mislorek et al. 2020, Seco-Cervera et al. 2018, Dantham et al. 2018, Mahishi et al. 2012			
	GSSG/GSH (oxidized/reduced glutathione)	n/a												
	Urinary isoprostanes	n/a									Myers et al. 2008			No difference between controls and FA
	Urinary 8-Oxo-dGuo	n/a									(Schulz et al. 2000)			
	Quality of Life measures (EQ-5D-5L, SF-36v2)	n/a									Epstein et al. 2008	MIN-102 (FRAMES) NCT03917225		These instruments can distinguish impact of FA compared to healthy controls however limited sensitivity to change over time.
	ENFD (epidermal nerve fiber density)	neuro									Hernandez et al. 2021			Some suggestion of change over 1 year, but not well tolerated, especially in children
	SSEP (somatosensory evoked potential)	neuro									Sival et al. 2009			Cannot be measured in most patients once symptomatic
	MEG - CKC (magnetoencephalography corticokinematic coherence)	neuro									Naeije et al. 2021			Not reproducible across different sites
	Sensory nerve conduction studies	neuro									Hernandez et al. 2021			Cannot be measured in most patients
	GaitRite measures	neuro									Milne et al. 2014			
	ICARS	neuro												Long and complex, multiple components not corresponding to the subscales. No advantage over FARS or SARA
	FAIS (Friedreich's Ataxia Impact Scale)	neuro									Tai et al. 2015, Cano et al. 2009			Showed little change over 2 years and only the speech component was significant
	Biodes Balance	neuro									Stephenson et al. 2015, Zesiewicz et al. 2017			Most measurements did not show any greater change over 1 year than 25-foot walk or FARS
	Functional composite (9HPT, 25FTW, Pah-1ah)	neuro									Lynch et al. 2005, Lynch et al. 2006, Friedman et al. 2010			Composites have some utility in assessing progression however regulatory feedback discourages use - question clinically meaningful change
	6 minute walk test	neuro												No because of fatigue and falls