Biomarkers and Endpoints for Friedreich's Ataxia

FARA has worked with the Friedreich's ataxia (FA) community through the years to help develop endpoints and biomarkers for use in clinical trials. The Collaborative Clinical Research Network for FA (CCRN) was initially formed to develop and test a neurological rating scale, the Friedreich's Ataxia Rating Scale, or FARS along with a disability rating scale, activities of daily living scale and functional measures[1,2,]. This scale is used to measure disease progression in patients, and a subscore (mFARS) has been accepted as an endpoint for late stage trials in FA. Data for this scale, alongside other outcomes, has now been collected by the CCRN for over 12 years[3]. Other rating scales and functional endpoints have also been used in trials, and data has been collected in natural history studies. More recently, a need for biomarkers for various contexts of use has been recognized, and data has been collected for a variety of such markers.

Neurological Exam Rating Scales: The FARS is the most common neurological rating scale used in the US[1], while the SARA (Scale for Assessment and Rating of Ataxia)[4] and ICARS (International Cooperative Ataxia Rating Scale)[5] scores are more commonly used in Europe[6]. These have all been used in trials and natural history studies, and the changes in the scales in various populations has been characterized. The US Food and Drug Administration (FDA) has worked with the FA community to consider the use of the FARS as an approvable endpoint in later stage clinical trials which has led to the modified FARS score, consisting of the specific neurological subscales that focus on patient function of the FARS score. This mFARS has been suggested as a possible approvable endpoint for some FA trials.

Functional Disability Rating and Activities of Daily Living: At the same time as the FARS was developed, two other measures for FA were created and tested to further quantify function outcomes and impact of disease. These have also been used in natural history studies and clinical trials. The functional disability rating scale is a clinician graded scale (0-6) that describes the severity of ataxia and impact on mobility. The Activities of Daily Living scale is a patient reported outcome measure that assesses impact of disease symptoms in 9 domains. In some studies and publications the FARS score has included all three of these measures combined into one score which has led to some confusion in comparing studies. These measures were not meant to be combined for scoring as they are measuring different things and should be scored and reported independently.

Functional Endpoints: Several functional endpoints have been assessed over time in FA. The 25-foot walk test[7] and the 9-hole peg test have been collected by the CCRN as a part of their natural history study, and have the most data surrounding them (over 10 years)[3]. However, recent studies have looked at more sophisticated measures of gait using the gaitrite system, balance using the Berg balance scale and Biodex balance system[8,9], use of accelerometers to look at daily activity, and several independent studies and early clinical trials have looked at exercise parameters as possible endpoints[10]. Other researchers have looked at specific tests for hearing (LiSNS), sight (low contrast visual acuity)[11] and speech (Vogel speech battery)[12].

Biomarkers: There has been a lot of effort into looking for sensitive biomarkers for FA. Systemic frataxin has been measured in trials using an ELISA system measuring protein levels in

blood and cheek swabs[13,14]. A recently developed mass spectrometry assay can differentiate different isoforms of frataxin and has improved sensitivity and specificity[15,16]. There is no current way to measure FXN levels in the central nervous system, but investigations are underway to use imaging to look at downstream affects. Other groups are looking at biomarkers for specific contexts of use as shown in Table 1.

Type of Measure	Measurement	Stage of Development	Papers published*?	Used in a trial?
PD/Response Biomarker – FXN upregulating drugs	FXN Mass spectrometry assay	Exploratory use in trials, additional longitudinal and cross sectional data needed.	Yes[15]	
	FXN ELISA	Exploratory use in trials, additional longitudinal and cross sectional data needed.	Yes[13,14]	Yes
Monitoring Biomarkers [neurological progression]	MRI -brain and spinal cord	Several small cross-sectional studies for both structural and functional imaging have been completed. Longitudinal data needed.	Yes[17,18]	
	Motor evoked potential	Preliminary data, studies ongoing.		
	Meissner Corpuscle imaging	Preliminary data, studies ongoing.		
	Nerve conduction	Preliminary data, studies ongoing.		
	Quantitative sensory testing	Preliminary data, studies ongoing.		
Monitoring Biomarkers [cardiac progression]	Cardiac MRI – Gadolinium staining	Preliminary data, studies ongoing.	Yes[19]	
	Serum biomarkers, Echo	Preliminary data, studies ongoing	Yes[19,20, 21]	
Response Biomarkers	Metabolic isotopologues in platelets,	Exploratory use in trials, additional longitudinal and cross sectional data needed.	Yes[22]	
	Cr-CEST	Exploratory use in trials, additional longitudinal and cross sectional data needed.	Yes[23]	
	MRS imaging	Exploratory use in trials, additional longitudinal and cross sectional data needed.	Yes[24]	
	Glucose and insulin, protein and gene expression panels	Further data collection and analysis needed.	Yes[25,2]	
Prognostic Biomarker – cardiac changes	Cardiac MRI – Gadolinium staining,	Preliminary data, studies ongoing.		

	Echo	Preliminary data, studies ongoing.		Yes
	Serum biomarkers	Preliminary data, studies ongoing.		Some, as safety markers
Outcome Measures	25-foot walk, 9 hole peg, balance and gait measures, accelerometry	25 foot walk and 9 hole peg have been used extensively, other studies ongoing, some may be ready for exploratory use soon	Yes[3,7,8,9]	25-ft walk, 9 hole peg
	Low contrast visual acuity	Exploratory use in trials, additional measures that quantify vision dysfunction are needed	Yes[11]	Yes
	LiSNS	Exploratory use in trials, additional longitudinal and cross sectional data needed	Yes[27]	Yes
	Vogel Speech battery	Exploratory use in trials, additional longitudinal and cross sectional data needed	Yes[12]	Yes
	Exercise testing	Studies ongoing, use in early phase trials	Yes[10]	Yes

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