CLAIMS

What is claimed is:

1. A method for evaluating efficacy of a frataxin (FXN) replacement therapy, the method comprising:

(a) determining a baseline FSLM(-) lipid profile for one or more FXN-sensitive lipid markers (FSLMs) in a sample obtained from an FXN deficient subject prior to administration of the FXN replacement therapy;

(b) determining an FXN replacement lipid profile for the one or more FXN-sensitive lipid markers (FSLMs) in a sample obtained from the FXN deficient subject following administration of the FXN replacement therapy;

(c) comparing the FXN replacement lipid profile determined in step (b) with the baseline FXN(-) lipid profile determined in step (a); and

(d) determining efficacy of the FXN replacement therapy based on the comparison in step (c);

wherein the one or more FSLMs are selected from a group consisting of:

triglycerides (TGs), wherein the three acyl groups in each triglyceride molecule contain less than 56 carbons and/or wherein the three acyl groups in each triglyceride molecule contain 7 or less unsaturations;

ether phospholipids;

phosphatidylcholines (PCs);

cholesteryl esters (CEs); and

diglycerides (DGs).

2. A method for evaluating efficacy of a frataxin (FXN) replacement therapy, the method comprising:

(a) determining an FXN replacement lipid profile for one or more FXN-sensitive lipid markers (FSLMs) in a sample obtained from an FXN deficient subject following administration of an FXN replacement therapy;

(b) comparing the subject FXN replacement lipid profile determined in step (a) with a reference FXN lipid profile for the one or more FSLMs; and

(c) determining efficacy of the FXN replacement therapy based on the comparison in step (b);

wherein the one or more FSLMs are selected from a group consisting of one or more of:

triglycerides (TGs), wherein the three acyl groups in each triglyceride molecule contain less than 56 carbons and/or wherein the three acyl groups in each triglyceride molecule contain 7 or less unsaturations;

ether phospholipids;

phosphatidylcholines (PCs);

cholesteryl esters (CEs); and

diglycerides (DGs).

3. The method of claim 2, wherein the reference FXN lipid profile is a baseline FXN(-) lipid profile for the one or more FSLMs; optionally, wherein the baseline FXN(-) lipid profile for the one or more FSLMs is determined in a sample obtained from an FXN deficient subject prior to administration of an FXN replacement therapy; further optionally

wherein the method further comprises determining a baseline FXN(-) lipid profile for the one or more FXN-sensitive lipid markers (FSLMs) in a sample obtained from the FXN deficient subject prior to administration of the FXN replacement therapy.

4. The method of any one of claims 1-3, wherein the one or more FSLMs are selected from a group consisting of:

(i) one or more triglycerides (TGs), wherein the three acyl groups in each triglyceride molecule contain less than 56 carbons and/or wherein the three acyl groups in each triglyceride molecule contain 7 or less unsaturations; optionally

wherein the one or more TGs are selected from the group consisting of TG45:1, TG46:1, TG46:3, TG47:1, TG47:2, TG48:0, TG48:1, TG48:2, TG48:3, TG49:1, TG49:2, TG49:3, TG49:4, TG50:1, TG50:2, TG50:3, TG50:4, TG50:5, TG51:1, TG51:2, TG51:3, TG51:4, TG52:2, TG52:3, TG52:4, TG52:5, TG52:6, TG53:2, TG53:3, TG53:4, TG53:5, TG54:4, TG54:5, TG54:6 and TG54:7; further optionally wherein the one or more FSLMs are selected from the group consisting of TG48:1, TG48:2, TG49:1, TG49:2, TG49:4, TG50:1, TG50:3, TG51:1, TG51:2, TG51:3, TG52:3 and TG53:2; or

(ii) one or more ether phospholipids; optionally wherein the one or more ether phospholipids comprise one or more ether diacylglycerophosphocholines (PCO-) or one or more phosphatidylethanolamine ethers (PEO-); further optionally

wherein the one or more PCO- are selected from the group consisting of PC(O-16:0/14:0), PC(O-16:0/18:2), PC(O-16:0/20:3), PC(O-16:0/20:4), PC(O-16:0/22:6), PC(O-17:0/20:4), PC(O-18:0/18:1), PC(O-18:0/22:6), PC(O-18:0/18:2), PC(O-18:1/18:2), PC(O-18:1/20:4), PC(O-18:1/20:5), PC(O-18:1/22:6), PC(O-(20:0/22:6), PC(O-20:1/22.6), PC(O-20:2/20:4), PC(O-22:2/20:4), PC(O-22:1/22:6), PC(O-22:2/20:4), PC(O-(24:1/22:6), PC(O-24:2/20:4), PCO-34:2, PCO-36:3, PCO-34:2, PCO-38:3, PCO-40:2, PCO-40:6, and PCO-44:7 and PCO-46.8; further optionally wherein the one or more PCO- are selected from the group consisting of PC(O-16:0/18:2), PC(O-16:0/20:3), PC(O-18:1/18:2). PC(O-22:2/20:4) and PC(O-24:2/20:4); or

(iii) one or more phosphatidylcholines (PCs); optionally

wherein the one or more PCs are selected from the group consisting of PC(15:0/20:3), PC(15:0/22:6), PC(16:0/14:0), PC(16:0/22:4), PC(16:1/16:0), PC(16:1/20:4), PC(16:1/22.5), PC(17:0/20:5), PC(18:0/20:3), PC(18:0/22:4), PC(18:1/20:3), PC(18:2/18:2), PC(20:4/15:0), PC40:6 and PC42:7; further optionally

wherein the one or more PCs are selected from the group consisting of PC(15:0/22:6) and PC(16:0/14:0); further optionally

wherein the one or more PCs are selected from the group consisting of PC(17:1/20:4), PC(18:2/18:3), PC(18:1/24:1), PC(18:2/20:5) and PC(20:4/20:0); further optionally

wherein the one or more PCs is PC(18:2/18:3); or

(iv) one or more cholesteryl esters (CEs); optionally

wherein the one or more CEs are selected from the group consisting of CE16:0 and CE20:5; optionally

wherein the one or more CEs is CE14:1; or

(v) one or more diglycerides (DGs); optionally

wherein the one or more DGs is DG18:1/18:2.

5. The method of any one of claims 1-4, wherein the amount of at least one or more FSLMs is increased in the subject following treatment with FXN replacement therapy; optionally

wherein the one or more FSLMs are selected from the group consisting of PC(O-16:0/14:0), PC(O-16:0/18:2), PC(O-16:0/20:3), PC(O-16:0/20:4), PC(O-16:0/22:6), PC(O-17:0/20:4), PC(O-18:0/18:1), PC(O-18:0/22:6), PC(O-18:0/18:2), PC(O-18:1/18:2), PC(O-18:1/20:4), PC(O-18:1/20:5), PC(O-18:1/22:6), PC(O-(20:0/22:6), PC(O-20:1/22.6), PC(O-20:2/20:4), PC(O-22:2/20:4), PC(O-22:1/22:6), PC(O-22:2/20:4), PC(O-(24:1/22:6), PC(O-24:2/20:4), PCO-34:2, PCO-36:3, PCO-34:2, PCO-38:3, PCO-40:2, PCO-40:6, and PCO-44:7, PCO-46.8, PC(17:1/20:4), PC(18:2/18:3), PC(18:1/24:1), PC(18:2/20:5), PC(20:4/20:0), CE16:0 and CE20:5; and/or

wherein the amount of at least one or more FSLMs is decreased in the subject following treatment with FXN replacement therapy; optionally wherein the one or more FSLMs are selected from the group consisting of TG45:1, TG46:1, TG46:3, TG47:1, TG47:2, TG48:0, TG48:1, TG48:2, TG48:3, TG49:1, TG49:2, TG49:3, TG49:4, TG50:1, TG50:2, TG50:3, TG50:4, TG50:5, TG51:1, TG51:2, TG51:3, TG51:4, TG52:2, TG52:3, TG52:4, TG52:5, TG52:6, TG53:2, TG53:3, TG53:4, TG53:5, TG54:4, TG54:5, TG54:6, TG54:7, PC(15:0/20:3), PC(15:0/22:6), PC(16:0/14:0), PC(16:0/22:4), PC(16:1/16:0),

PC(16:1/20:4), PC(16:1/22.5), PC(17:0/20:5), PC(18:0/20:3), PC(18:0/22:4), PC(18:1/20:3), PC(18:2/18:2), PC(20:4/15:0), PC40:6, PC42:7, DG18:1/18:2 and CE14:1.

6. The method of any one of claims 1-5, wherein determining an FXN lipid profile for one or more FSLMs comprises determining the amount of the one or more FSLMs; optionally

wherein comparing the subject FXN replacement lipid profile with the baseline FXN(-) lipid profile comprises comparing the amount of one or more FSLMs in the FXN replacement lipid profile with the amount of the corresponding one or more FSLMs in the baseline FXN(-) lipid profile.

7. The method of claim 6, wherein the FXN replacement therapy is determined to be effective when the amount of one or more FSLMs is increased in the FXN replacement lipid profile as compared to the baseline FXN(-) lipid profile,

wherein the one or more FSLMs are selected from the group consisting of PC(O-16:0/14:0), PC(O-16:0/18:2), PC(O-16:0/20:3), PC(O-16:0/20:4), PC(O-16:0/22:6), PC(O-17:0/20:4), PC(O-18:0/18:1), PC(O-18:0/22:6), PC(O-18:0/18:2), PC(O-18:1/18:2), PC(O-18:1/20:4), PC(O-18:1/20:5), PC(O-18:1/22:6), PC(O-(20:0/22:6), PC(O-20:1/22.6), PC(O-20:2/20:4), PC(O-22:2/20:4), PC(O-22:1/22:6), PC(O-22:2/20:4), PC(O-(24:1/22:6), PC(O-24:2/20:4), PCO-34:2, PCO-36:3, PCO-34:2, PCO-38:3, PCO-40:2, PCO-40:6, and PCO-44:7, PCO-46.8, PC(17:1/20:4), PC(18:2/18:3), PC(18:1/24:1), PC(18:2/20:5), PC(20:4/20:0), CE16:0 and CE20:5; or

wherein the FXN replacement therapy is determined to be effective when the amount of one or more FSLMs is decreased in the FXN replacement lipid profile as compared to the baseline FXN(-) lipid profile, wherein the one or more FSLMs are selected from the group consisting of TG45:1, TG46:1, TG46:3, TG47:1, TG47:2, TG48:0, TG48:1, TG48:2, TG48:3, TG49:1, TG49:2, TG49:3, TG49:4, TG50:1, TG50:2, TG50:3, TG50:4, TG50:5, TG51:1, TG51:2, TG51:3, TG51:4, TG52:2, TG52:3, TG52:4, TG52:5, TG52:6, TG53:2, TG53:3, TG53:4, TG53:5, TG54:4, TG54:5, TG54:6, TG54:7, PC(15:0/20:3), PC(15:0/22:6), PC(16:0/14:0), PC(16:0/22:4), PC(16:1/16:0), PC(16:1/20:4), PC(16:1/22.5), PC(17:0/20:5), PC(18:0/20:3), PC(18:0/22:4), PC(18:1/20:3), PC(18:2/18:2), PC(20:4/15:0), PC40:6, PC42:7, DG18:1/18:2 and CE14:1.

8. The method of any one of claims 1-7, wherein determining an FXN lipid profile for one or more FSLMs comprises determining an FXN lipid feature vector of values indicative of lipid of the one or more FSLMs; optionally

wherein determining efficacy of the FXN replacement therapy comprises determining a first FXN lipid feature vector for the subject FXN replacement lipid profile and a second FXN lipid feature vector for the baseline FXN (-) lipid profile and determining a distance between the first and second lipid feature vectors; optionally

wherein determining the distance between the lipid feature vectors comprises determining a scalar product of the first and second lipid feature vectors.

9. The method of claim 8, further comprising

determining a third lipid feature vector for a normal FXN lipid profile for the FSLMs for a healthy subject; optionally comprising determining a distance between the second and third lipid feature vectors; further optionally comprising determining a distance between the first and third lipid feature vectors, and normalizing the distance between the first and third lipid feature vectors to the distance between the second and third lipid feature vectors; further optionally comprising using the normalized distance to determine effectiveness of the FXN replacement therapy.

10. The method of any one of claims 1-9, wherein the FXN lipid profile is determined by mass spectrometry.

11. The method of any one of claims 1-10, further comprising recommending to a healthcare provider to modify the treatment with the FXN replacement therapy based on the determination of efficacy for the FXN replacement therapy.

12. The method of any one of claims 1-11, wherein the subject has Friedreich’s Ataxia (FRDA).

13. The method of any one of claims 1-12, wherein a sample is to be further obtained from the FXN deficient subject; optionally

wherein the sample is selected from the group consisting of a buccal sample, a skin sample, a hair follicle or a blood-derived sample; further optionally

wherein the sample is a blood-derived sample; further optionally

wherein the blood-derived sample is a plasma sample.

14. A method of monitoring treatment of a subject with a frataxin (FXN) replacement therapy, the method comprising:

(a) determining a first FXN replacement lipid profile for one or more FXN-sensitive lipid markers (FSLMs) in a first sample obtained from an FXN deficient subject at a first time point following administration of an FXN replacement therapy to the subject,

(b) determining a second FXN replacement lipid profile for the one or more FXN-sensitive lipid markers (FSLMs) in a second sample obtained from the subject at a second time point that is later than the first time point;

(c) comparing the second FXN replacement lipid profile with the first FXN replacement profile; thereby monitoring treatment of the subject with the FXN replacement therapy;

wherein the one or more FSLMs are selected from a group consisting of one or more of:

triglycerides (TGs), wherein the three acyl groups in each triglyceride molecule contain less than 56 carbons and/or wherein the three acyl groups in each triglyceride molecule contain 7 or less unsaturations;

ether phospholipids;

phosphatidylcholines (PCs)

cholesteryl esters (CEs); and

diglycerides (DGs).

15. The method of claim 14, further comprising making a determination to maintain, increase or decrease the dose or administration frequency of the FXN replacement therapy based on the comparison in step (c).

16. The method of claim 14 or 15,

wherein at least one dose of the FXN replacement therapy is to be administered to the subject between obtaining the first time point and second time point; and/or

wherein the FXN replacement therapy is not to be administered to the subject between obtaining the first time point and second time point.

17. The method of any one of claims 14-16,

wherein the one or more FSLMs are selected from a group consisting of:

(i) one or more triglycerides (TGs), wherein the three acyl groups in each triglyceride molecule contain less than 56 carbons and/or wherein the three acyl groups in each triglyceride molecule contain 7 or less unsaturations; optionally wherein the one or more TGs are selected from the group consisting of TG45:1, TG46:1, TG46:3, TG47:1, TG47:2, TG48:0, TG48:1, TG48:2, TG48:3, TG49:1, TG49:2, TG49:3, TG49:4, TG50:1, TG50:2, TG50:3, TG50:4, TG50:5, TG51:1, TG51:2, TG51:3, TG51:4, TG52:2, TG52:3, TG52:4, TG52:5, TG52:6, TG53:2, TG53:3, TG53:4, TG53:5, TG54:4, TG54:5, TG54:6 and TG54:7; or

(ii) one or more ether phospholipids; optionally, wherein the one or more ether phospholipids comprise one or more ether diacylglycerophosphocholines (PCO-) or one or more phosphatidylethanolamine ethers (PEO-); further optionally wherein the one or more PCO- are selected from the group consisting of PC(O-16:0/14:0), PC(O-16:0/18:2), PC(O-16:0/20:3), PC(O-16:0/20:4), PC(O-16:0/22:6), PC(O-17:0/20:4), PC(O-18:0/18:1), PC(O-18:0/22:6), PC(O-18:0/18:2), PC(O-18:1/18:2), PC(O-18:1/20:4), PC(O-18:1/20:5), PC(O-18:1/22:6), PC(O-(20:0/22:6), PC(O-20:1/22.6), PC(O-20:2/20:4), PC(O-22:2/20:4), PC(O-22:1/22:6), PC(O-22:2/20:4), PC(O-(24:1/22:6), PC(O-24:2/20:4), PCO-34:2, PCO-36:3, PCO-34:2, PCO-38:3, PCO-40:2, PCO-40:6, and PCO-44:7 and PCO-46.8; or

(iii) one or more phosphatidylcholines (PCs); optionally wherein the one or more PCs are selected from the group consisting of PC(15:0/20:3), PC(15:0/22:6), PC(16:0/14:0), PC(16:0/22:4), PC(16:1/16:0), PC(16:1/20:4), PC(16:1/22.5), PC(17:0/20:5), PC(18:0/20:3), PC(18:0/22:4), PC(18:1/20:3), PC(18:2/18:2), PC(20:4/15:0), PC40:6, PC42:7, PC(17:1/20:4), PC(18:2/18:3), PC(18:1/24:1), PC(18:2/20:5) and PC(20:4/20:0); or

(iv) one or more cholesteryl esters (CEs); optionally wherein the one or more CEs are selected from the group consisting of CE14:1, CE16:0 and CE20:5; or

(v) one or more diglycerides (DGs); optionally wherein the one or more DGs is DG18:1/18:2.

18. Use of an FXN replacement therapy in the manufacture of a medicament for treating an FXN deficiency, the use comprising:

(a) determining an FXN lipid profile in a sample obtained from an FXN deficient subject for one or more FXN-sensitive lipid markers (FSLMs),

(b) comparing the FXN lipid profile of the sample with at least one other lipid profile selected from the group consisting of normal FXN lipid profile for the one or more FSLMs, baseline FXN(-) lipid profile for the one or more FSLMs, and FXN replacement lipid profile for the one or more FSLMs,

(c) classifying the FXN lipid profile determined in step (a) as corresponding to a normal FXN lipid profile, baseline FXN(-) lipid profile or an FXN replacement lipid profile, and

(d) initiating or modulating an FXN replacement therapy based on the classification of the FXN lipid profile of the sample.

19. The use of claim 18, wherein modulating an FXN replacement therapy comprises increasing the dosage, decreasing the dosage, increasing the administration frequency, or decreasing the administration frequency, of the FXN replacement therapy; and/or

wherein the FXN deficient subject has Friedreich's Ataxia (FRDA).

20. A method of detecting one or more frataxin-sensitive lipid markers (FSLMs) in a sample from a frataxin (FXN) deficient subject, comprising

contacting the sample, or a portion thereof, with one or more reagents specific for detecting the level of each of the one or more FSLMs; or

subjecting the sample, or a portion thereof, to analysis by mass spectrometry.

21. The method of any one of claims 18-20, wherein the one or more FSLMs are selected from a group consisting of:

triglycerides (TGs), wherein the three acyl groups in each triglyceride molecule contain less than 56 carbons and/or wherein the three acyl groups in each triglyceride molecule contain 7 or less unsaturations;

ether phospholipids;

phosphatidylcholines (PCs);

cholesteryl esters (CEs); and

diglycerides (DGs).

22. The method of claim 21, wherein the one or more FSLMs are selected from a group consisting of:

(i) one or more triglycerides (TGs), wherein the three acyl groups in each triglyceride molecule contain less than 56 carbons and/or wherein the three acyl groups in each triglyceride molecule contain 7 or less unsaturations; optionally wherein the one or more TGs are selected from the group consisting of TG45:1, TG46:1, TG46:3, TG47:1, TG47:2, TG48:0, TG48:1, TG48:2, TG48:3, TG49:1, TG49:2, TG49:3, TG49:4, TG50:1, TG50:2, TG50:3, TG50:4, TG50:5, TG51:1, TG51:2, TG51:3, TG51:4, TG52:2, TG52:3, TG52:4, TG52:5, TG52:6, TG53:2, TG53:3, TG53:4, TG53:5, TG54:4, TG54:5, TG54:6 and TG54:7; or

(ii) one or more ether phospholipids; optionally, wherein the one or more ether phospholipids comprise one or more ether diacylglycerophosphocholines (PCO-) or one or more phosphatidylethanolamine ethers (PEO-); optionally wherein the one or more PCO- are selected from the group consisting of PC(O-16:0/14:0), PC(O-16:0/18:2), PC(O-16:0/20:3), PC(O-16:0/20:4), PC(O-16:0/22:6), PC(O-17:0/20:4), PC(O-18:0/18:1), PC(O-18:0/22:6), PC(O-18:0/18:2), PC(O-18:1/18:2), PC(O-18:1/20:4), PC(O-18:1/20:5), PC(O-18:1/22:6), PC(O-(20:0/22:6), PC(O-20:1/22.6), PC(O-20:2/20:4), PC(O-22:2/20:4), PC(O-22:1/22:6), PC(O-22:2/20:4), PC(O-(24:1/22:6), PC(O-24:2/20:4), PCO-34:2, PCO-36:3, PCO-34:2, PCO-38:3, PCO-40:2, PCO-40:6, and PCO-44:7 and PCO-46.8; or

(iii) one or more phosphatidylcholines (PCs); optionally wherein the one or more PCs are selected from the group consisting of PC(15:0/20:3), PC(15:0/22:6), PC(16:0/14:0), PC(16:0/22:4), PC(16:1/16:0), PC(16:1/20:4), PC(16:1/22.5), PC(17:0/20:5), PC(18:0/20:3), PC(18:0/22:4), PC(18:1/20:3), PC(18:2/18:2), PC(20:4/15:0), PC40:6, PC42:7, PC(17:1/20:4), PC(18:2/18:3), PC(18:1/24:1), PC(18:2/20:5) and PC(20:4/20:0); or

(iv) one or more cholesteryl esters (CEs); optionally wherein the one or more CEs are selected from the group consisting of CE14:1, CE16:0 and CE20:5; or

(v) one or more diglycerides (DGs); optionally, wherein the one or more DGs is DG18:1/18:2.

23. The method of any one of claims 14-17 and 20-22 or the use of claim 18 or 19,

wherein the FXN lipid profile is determined by mass spectrometry; and/or

wherein the subject has Friedreich's Ataxia (FRDA).

24. The method of any one of claims 14-17 and 20-23 or the use of claim 18 or 19, wherein a sample is to be further obtained from the FXN deficient subject; optionally

wherein the sample is selected from the group consisting of a buccal sample, a skin sample, a hair follicle or a blood-derived sample; further optionally

wherein the sample is a blood-derived sample; further optionally

wherein the blood-derived sample is a plasma sample.

25. The method of any one of claims 1-17 and 21-24 or the use of claim 18 or 19, wherein the FXN replacement therapy comprises administration of an FXN fusion protein; optionally, wherein the FXN fusion protein comprises or consists of the amino acid sequence set forth in SEQ ID NO: 12.

26. A kit for detecting one or more frataxin-sensitive lipid markers (FSLMs) in a sample obtained from a frataxin (FXN) deficient subject, comprising

one or more isotopically labeled lipids for use as internal standards in a mass spectrometry-based analysis for detecting one or more FSLMs in the sample, and

a set of instructions for detecting the level of the one or more FSLMs in the sample from the subject by mass spectrometry.

27. The method of any one of claims 1-17 and 20-26 or the use of claim 18 or 19, wherein the subject is a human.