Supplementary table 1

Diagnostic criteria for a definite diagnosis of FD (adopted from Smid et al with permission [1]).

<table>
<tr><th colspan="2">Definite diagnosis of FD</th></tr>
<tr><td>Males
GLA variant
+
αGalA deficiency of ≤5% of mean reference value in leukocytes
+</td><td>Females
GLA variant
+
normal or deficient αGalA in leukocytes
+</td></tr>
<tr><td colspan="2">A or B or C
A
≥1 characteristic FD sign/symptom (Fabry neuropathic pain, cornea verticillata or clustered angiokeratoma)
B
an increase of plasma (lyso)Gb3 (within range of males with definite FD diagnosis)
C
A family member with a definite FD diagnosis carrying the same GLA variant</td></tr>
<tr><th colspan="2">Uncertain diagnosis of FD</th></tr>
<tr><td colspan="2">Males/Females
All patients presenting with a non-specific FD sign (such as LVH, stroke at young age, proteinuria) who do not fulfil the criteria for a definite diagnosis of FD have a GLA GVUS. Further evaluations are needed, following diagnostic algorithms**.</td></tr>
<tr><th colspan="2">Gold standard for uncertain FD diagnoses</th></tr>
<tr><td colspan="2">In subjects with an uncertain FD diagnosis, a GVUS and a non-specific FD sign, the demonstration of characteristic storage in the affected organ (e.g. heart, kidney, aside from skin) by electron microscopy analysis, according to the judgment of an expert pathologist, in the absence of medication that can lead to storage, confirms FD.</td></tr>
</table>

***Definitions:**

Fabry neuropathic pain meets the 'characteristic clinical criteria' if there is neuropathic pain in hands and/or feet, starting before age 18 years or increasing with heat, fever. Quantitative sensory testing (QST) reveals a decreased cold detection threshold and the intraepidermal nerve fiber density is increased. There is no other cause for neuropathic pain.

Angiokeratoma meet the 'characteristic clinical criteria' if they are clustered and present in characteristic areas: bathing trunk area, lips, and umbilicus. There is no other cause for angiokeratoma.

Cornea verticillata meets the 'characteristic clinical criteria' if there is a whorl like pattern of corneal opacities. There is no other cause (medication induced, among other: amiodarone, chloroquine).

Abbreviations: GLA: α-Galactosidase A gene, αGalA: α-Galactosidase A enzyme, GVUS: genetic variant of unknown significance.

**For organ specific algorithms see Smid et al [1] and Van der Tol et al [2 3].

1. Smid BE, van der Tol L, Cecchi F, et al. Uncertain diagnosis of Fabry disease: Consensus recommendation on diagnosis in adults with left ventricular hypertrophy and genetic variants of unknown significance. International journal of cardiology 2014;**177**(2):400-08
2. van der Tol L, Svarstad E, Ortiz A, et al. Chronic kidney disease and an uncertain diagnosis of Fabry disease: Approach to a correct diagnosis. Mol Genet Metab 2014 epub ahead of print.
3. van der Tol L, Üçeyler N, Burlina A et al. The value of specific brain imaging characteristics in the diagnosis of Fabry disease 2014;submitted.