### 1. Disorder/condition – approved name and symbol as published on the OMIM database (alternative names will be listed on the UKGTN website)

If this submission is for a panel test please complete appendix 1 listing all of the conditions included using approved OMIM name, symbol and OMIM number.

**LYSOSOMAL ACID LIPASE DEFICIENCY**

#### 2. OMIM number for disorder/condition

If a panel test – see 1. above

278000

#### 3a. Disorder/condition – please provide, in laymen’s terms, a brief (2-5 sentences) description of how the disorder(s) affect individuals and prognosis.

Lysosomal acid lipase (LAL) deficiency is a lipid storage disease that can result in:-

1. An early onset form, Wolman disease, which is fatal in the first year of life.
2. A less severe form, cholesteryl ester storage disease (CESD). Leads to liver disease/failure and an increased risk of strokes because of potential build up of lipid in the walls of the major arteries (atherosclerosis).

#### 3b. Disorder/condition – if required please expand on the description of the disorder provided in answer to Q3a.

Wolman disease is characterised by neonatal abdominal distension, major or massive hepatosplenomegaly and calcified adrenal glands. Death occurs early in life. Wolman disease is very rare, with an incidence of less than one in 100,000 live births.

CESD is a milder, later-onset disorder with primary liver involvement by macrophages engorged with cholesteryl esters. This slowly progressive visceral disease has a very wide spectrum of involvement ranging from early onset with severe cirrhosis to later onset of more slowly progressive liver failure and atherosclerosis.

LAL deficiency is a serious and life threatening disease, and there are currently no approved treatments.

#### 4. Disorder/condition – mode of inheritance

If this submission is for a panel test, please complete the mode of inheritance for each condition in the table in appendix 1.

Autosomal recessive

#### 5. Gene – approved name(s) and symbol as published on HGNC database (alternative names will be listed on the UKGTN website)

If this submission is for a panel test please complete appendix 1 listing all of the genes included using approved HGNC name, symbol, number and OMIM number.

lipase A, lysosomal acid, cholesterol esterase; LIPA

#### 6a. OMIM number(s) for gene(s)

If a panel test – see 5. above

613497

#### 6b. HGNC number(s) for gene(s)

If a panel test – see 5. above

6617
7a. Gene – description(s)
If this submission is for a panel test, please provide total number of genes.

LAL is encoded by LIPA located on chromosome 10: 10q23.2-q23.3. The LIPA gene is 36kb in length and has 10 exons. The most common mutation associated with CESD is an exon 8 splice junction mutation (c.894G>A:E8SJM).

7b. Number of amplicons to provide this test (molecular) or type of test (cytogenetic)
(n/a for panel tests)

10

7c. GenU band that this test is assigned to for index case testing.

Band E (10 GenU)

8. Mutational spectrum for which you test including details of known common mutations
(n/a for panel tests)
If this application is for a panel test to be used for different clinical phenotypes and/or various sub panel tests – please contact the team for advice before completing a Gene Dossier

>20 mutations in LIPA have been found to cause CESD and 10 mutations in LIPA have been found to cause Wolmans disease. These mutations include missense, nonsense, splice site, small insertions/deletions. We perform Sanger sequencing of all exons which would pick up the vast majority of these mutations.

9a. Technical method(s) – please describe the test.

PCR and bi-directional Sanger sequencing of all exons and intron/exon boundaries from extracted DNA. Nested PCR and Sanger sequencing of all exons and intron/exon boundaries from dried blood spots.

9b. For panel tests, please specify the strategy for dealing with gaps in coverage.

N/A

9c. Does the test include MLPA?
(For panel tests, please provide this information in appendix 1)

No

9d. If NGS is used, does the lab adhere to the Association of Clinical Genetic Science Best Practice Guidelines for NGS?

N/A

10. Is the assay to be provided by the lab or is it to be outsourced to another provider?
If to be outsourced, please provide the name of the laboratory and a copy of their ISO certificate or their CPA number.

Assay will be provided by this laboratory

11. Validation process
Please explain how this test has been validated for use in your laboratory or submit your internal validation documentation. If this submission is for a panel test, please provide a summary of evidence of:

i) instrument and pipeline validation, and
ii) panel verification for the test

Please submit as appendices to the Gene Dossier (these will be included in the published Gene Dossier available on the website).

Please note that the preferred threshold for validation and verification is 95% sensitivity with 95% Confidence Intervals.

Sequencing is a standard analytical method used in the laboratory for a range of diagnostic services requiring mutation detection. Analysis is conducted in accordance with CPA standards for which we are fully accredited.
**12a. Are you providing this test already?**
Yes

**12b(i). If yes, how many reports have you produced?**
- 8 diagnostic tests
- 5 carrier tests
- 2 predictive tests

**12b(ii). Number of reports mutation positive?**
5 diagnostic tests with mutations (all of which had enzyme deficiency)

**12b(iii). Number of reports mutation negative?**
3 diagnostic tests with no mutation (no enzyme testing done)

**12b(iv). Please provide the time period in which these reports have been produced and whether in a research or a full clinical diagnostic setting.**
Service available since 2011 in clinical diagnostic setting

**13a. Is there specialised local clinical/research expertise for this disorder?**
Yes

**13b. If yes, please provide details**
We work closely with the Centre for Inherited Metabolic Diseases at the Evelina London Children’s Hospital. There are currently 5 consultants specialising in inherited metabolic diseases, including the lysosomal storage diseases.

We also carry out lysosomal acid lipase enzyme analysis in this laboratory. Our laboratory specialises in lysosomal storage disorders: we test for many (30+) by enzymology and also several by molecular genetic techniques.

**14. Based on experience what will be the national (UK wide) activity, per annum, for:**

<table>
<thead>
<tr>
<th>Index cases</th>
<th>10 per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family members where mutation is known</td>
<td>25 per year</td>
</tr>
</tbody>
</table>

**15. If your laboratory does not have capacity to provide the full national need please suggest how the national requirement may be met.**
For example, are you aware of any other labs (UKGTN members or otherwise) offering this test to NHS patients on a local area basis only? This question has been included in order to gauge if there could be any issues in equity of access for NHS patients. If you are unable to answer this question please write “unknown”.

We would have sufficient capacity to provide the number of tests expected per annum.

**16. If using this form as an Additional Provider application, please explain why you wish to provide this test as it is already available from another provider.**
## EPIDEMIOLOGY

### 17a. Estimated prevalence of conditions in the general UK population

Prevalence is total number of persons with the condition(s) in a defined population at a specific time. Please identify the information on which this is based.

For panel tests, please provide estimates for the conditions grouped by phenotypes being tested.

Pan-ethnic but worldwide prevalence is not known.

Guy’s & St Thomas’ has one of the largest IMD centres in the UK and currently has contact with less than 10 patients with LAL deficiency.

Higher incidence has been described in the Iranian-Jewish population.

### 17b. Estimated annual incidence of conditions in the general UK population

Incidence is total number of new cases in a year in a defined population. Please identify the information on which this is based.

For panel tests, please provide for groups of conditions.

No reliable figures can be identified. Limited information as this disorder is extremely rare. Publications and databases such as OMIM state following figures: Wolman’s disease affects 1 – 2 babies for every million births. CESD affects 25 individuals per million births.

### 18. Estimated gene frequency (Carrier frequency or allele frequency)

Please identify the information on which this is based.

n/a for panel tests.

Carrier frequency 1/100.

### 19. Estimated penetrance of the condition.

Please identify the information on which this is based

n/a for panel tests.

Close to 100% in patients with clinical symptoms and lysosomal acid lipase deficiency

### 20. Estimated prevalence of conditions in the population of people that will be tested.

n/a for panel tests.

See above – all patients should have enzyme testing.

## INTENDED USE

(Please use the questions in Annex A to inform your answers)

### 21. Please tick either yes or no for each clinical purpose listed.

**Panel Tests:** a panel test would not be used for pre symptomatic testing, carrier testing and pre natal testing as the familial mutation would already be known in this case and the full panel would not be required.

<table>
<thead>
<tr>
<th>Clinical Purpose</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td><strong>Prognosis &amp; management</strong></td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td><strong>Presymptomatic testing</strong></td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td><strong>Carrier testing for family members</strong></td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td><strong>Prenatal testing</strong></td>
<td>✔️</td>
<td></td>
</tr>
</tbody>
</table>
### TEST CHARACTERISTICS

#### 22. Analytical sensitivity and specificity

This should be based on your own laboratory data for the specific test being applied for or the analytical sensitivity and specificity of the method/technique to be used in the case of a test yet to be set up.

Please note that the preferred threshold for validation and verification is 95% sensitivity with 95% Confidence Intervals.

Sensitivity: Bi-directional Sanger sequencing of all exons and intron-exon boundaries. A CMGS study indicates Sanger sequencing in combination with Mutation Surveyor software has a sensitivity of >99.59% sensitivity. Other mutation types are possible (e.g. large deletions, promoter region, intronic) however there is insufficient evidence to suggest additional testing is required.

Specificity: Close to 100% in biochemically normal individuals although limited testing has been carried out and unclassified variants are possible.

#### 23. Clinical sensitivity and specificity of test in target population

The clinical sensitivity of a test is the probability of a positive test result when condition is known to be present; the clinical specificity is the probability of a negative test result when disorder is known to be absent. The denominator in this case is the number with the disorder (for sensitivity) or the number without condition (for specificity).

Please provide the best estimate. UKGTN will request actual data after two years service.

Sensitivity: All patients with lysosomal acid lipase deficiency would be expected to have mutations in the LIPA gene.

Specificity: Close to 100% in biochemically normal individuals although limited testing has been carried out and unclassified variants are possible.

#### 24. Clinical validity (positive and negative predictive value in the target population)

The clinical validity of a genetic test is a measure of how well the test predicts the presence or absence of the phenotype, clinical condition or predisposition. It is measured by its positive predictive value (the probability of getting the condition given a positive test) and negative predictive value (the probability of not getting the condition given a negative test).

Not currently requested for panel tests

#### 25. Testing pathway for tests where more than one gene is to be tested sequentially

Please include your testing strategy if more than one gene will be tested and data on the expected proportions of positive results for each part of the process. Please illustrate this with a flow diagram. This will be added to the published Testing Criteria.

n/a for panel tests

### CLINICAL UTILITY

#### 26. How will the test change the management of the patient and/or alter clinical outcome?

Please describe associated benefits for patients and family members. If there are any cost savings AFTER the diagnosis, please detail them here.

Confirmation of biochemical and clinical diagnosis to inform carrier testing and reproductive choices in these severe disorders which cannot be done on the basis of biochemical basis alone.

Carrier testing for family members and prenatal diagnosis.

There is no definitive treatment for this disorder. A number of supportive therapies are used to try to slow the progress of the disease, including special diets and drugs for disease complications. Cholesterol lowering drugs (statins and/or ezetimide) may be prescribed for children and adults with CESD, because of high level of cholesterol and other fats in the blood, but may not be successful in improving already severe liver manifestations. Liver transplantation has been performed in some
severe cases. Early confirmation of the diagnosis is therefore essential, before the disease has progressed to unmanageable state.

27. If this test was not available, what would be the consequences for patients and family members?

Enzyme testing cannot be used to identify carriers of these conditions. Prenatal diagnosis: parents who have had a severely affected child may request a molecular prenatal in subsequent pregnancies. Hence molecular testing is essential in the proband.

The option of pre-implantation genetic diagnosis (PGD) can only be carried out if the mutations in the family are known.

It would not be possible to offer carrier testing to other family members. Relatives may opt to have prenatal diagnosis using enzyme assay: this may not be necessary if both partners are not carriers.

If this test is not available more affected individuals may be born in families, or alternatively partners may undergo unnecessary prenatal testing by enzymology.

This test will enable cascade screening to be offered in families in order to detect individuals with the milder, later onset forms of the disorder. If detected earlier the progression can be managed more effectively.

28. Is there an alternative means of diagnosis or prediction that does not involve molecular diagnosis? If so (and in particular if there is a biochemical test), please state the added advantage of the molecular test.

Biochemical testing of enzyme activity is available for this disorder and offered in our laboratory. This should be carried out as a first line test and the result then confirmed by molecular analysis. Enzyme analysis cannot be used for carrier testing.

29a. What unexpected findings could this test show? For example, lung cancer susceptibility when testing for congenital cataract because ERCC6 gene (primarily associated with lung cancer) is included in a panel test for congenital cataract.

None

29b. Please list any genes where the main phenotype associated with that gene is unrelated to the phenotype being tested by the panel.

N/A

30. If testing highlights a condition that is very different from that being tested for, please outline your strategy for dealing with this situation.

N/A

31. If a panel test, is this replacing an existing panel/multi gene test and/or other tests currently carried out through UKGTN using Sanger sequencing? If so, please provide details below.

N/A

32. Please describe any specific ethical, legal or social issues with this particular test.

None
### IS IT A REASONABLE COST TO THE PUBLIC?

33. In order to establish the potential costs/savings that could be realised in the diagnostic care pathway, please list the tests/procedures that would be required in the index case to make a diagnosis if this genetic test was not available.

<table>
<thead>
<tr>
<th>Costs and type of imaging procedures</th>
<th>Type of test</th>
<th>Cost (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs and types of laboratory pathology tests (other than molecular/cyto genetic test proposed in this Gene Dossier)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costs and types of physiological tests (e.g. ECG)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost and types of other investigations/procedures (e.g. biopsy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total cost of tests/procedures no longer required</strong> (please write n/a if the genetic test does not replace any other tests procedures in the diagnostic care pathway)</td>
<td></td>
<td>N/A</td>
</tr>
</tbody>
</table>

34. Based on the expected annual activity of index cases (Q14), please calculate the estimated annual savings/investments based on information provided in Q33.

| Number of index cases expected annually | (a) 10 |
| Cost to provide tests for index cases if the genetic test in this Gene Dossier was not available (see Q32) | (b) |
| **Total annual costs pre genetic test** | (a) x (b) = (c) |
| **Total annual costs to provide genetic test** | (a) 10 x £375 cost of genetic testing for index case = (d) £3750 |
| Additional investment for 100% positive rate for index cases | (d) – (c) = (e) £3750 |
| Percentage of index cases estimated to be negative | (f) |
| Number of index cases estimated to be negative | (f) x number of index cases = (g) |
| **Costs to provide additional tests for index cases testing negative** | (g) x (b) = (h) |
| **Total costs for tests for index patient activity** | (e) + (h) = (i) £3750 |
| **Total costs for family members** | Costs for family member test x number of family members expected to test in a year (j) £160 x 25 = £4000 |
| If there is a genetic test already available and some of the family testing is already being provided, please advise the cost of the family testing already available | Cost for family member testing already available x estimated number of tests for family members already provided (k) |
| **Total costs for family members minus any family member testing costs already provided** | (j) – (k) = (l) |
| **Additional costs for all activity expected in a year** | £3750 + £4000 = £7,750 |

### 35. REAL LIFE CASE STUDY
Please provide a case study that illustrates the benefits of this test

The proband is the first child of consanguineous parents. He had a history of abdominal distention and severe faltering growth. He was noted to have marked hepatosplenomegaly and in view of liver dysfunction and ascites was referred to a specialist centre.
At the specialist centre he was noted to be jaundiced with conjugated hyperbilirubinaemia, liver dysfunction and respiratory difficulties. A bone marrow aspirate was performed and showed the presence of storage cells consistent with a lysosomal storage disorder. The diagnosis of Wolman’s disease was confirmed when the white cell enzyme assay revealed low levels of lysosomal acid lipase activity.

There was no active treatment available for this severe disorder and the palliative team became involved in his care. It was decided not to perform any further invasive tests and to keep him comfortable during his short life.

The parents and the extended family were understandably devastated with this news. However, having confirmation of the diagnosis enabled the health care professionals involved to provide appropriate care and support to the affected child and family members.

Having this genetic test will give parents the option of prenatal diagnosis or pre-implantation genetic diagnosis for future family planning. This information will also be helpful for carrier testing appropriate family members. Without this test it is not possible to offer carrier testing to other at-risk family members, and further affected individuals may be born.

### TESTING CRITERIA

36. Please only complete this question if there is previously approved Testing Criteria. Please contact the UKGTN office if you are unsure whether testing criteria is available.

36a. Do you agree with the previously approved Testing Criteria? Yes/No

36b. If you do not agree, please provide revised Testing Criteria on the Testing Criteria form and explain below the reasons for the changes.
# UKGTN Testing Criteria

**Test name:**
Lysosomal Acid Lipase Deficiency

<table>
<thead>
<tr>
<th>Approved name and symbol of disorder/condition(s):</th>
<th>OMIM number(s):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lysosomal Acid Lipase (LAL) Deficiency</td>
<td>27800</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Approved name and symbol of gene(s):</th>
<th>OMIM number(s):</th>
</tr>
</thead>
<tbody>
<tr>
<td>lipase A, lysosomal acid, cholesterol esterase; LIPA</td>
<td>613497</td>
</tr>
</tbody>
</table>

**Patient name:**

**Date of birth:**

**Patient postcode:**

**NHS number:**

**Name of referrer:**

**Title/Position:**

**Lab ID:**

**Referrals will only be accepted from one of the following:**

<table>
<thead>
<tr>
<th>Referrer</th>
<th>Tick if this refers to you.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultant Clinical Geneticist</td>
<td></td>
</tr>
<tr>
<td>Consultant Metabolic Disease Specialist</td>
<td></td>
</tr>
<tr>
<td>Consultant Chemical Pathologist</td>
<td></td>
</tr>
<tr>
<td>Consultant Lipidologist</td>
<td></td>
</tr>
</tbody>
</table>

**Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Tick if this patient meets criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient with LAL enzyme deficiency</td>
<td></td>
</tr>
<tr>
<td>At risk family members where familial mutation is known.</td>
<td></td>
</tr>
</tbody>
</table>

**Additional Information:**

If the sample does not fulfil the clinical criteria or you are not one of the specified types of referrer and you still feel that testing should be performed please contact the laboratory to discuss testing of the sample.

**Approval Date:** September 2014

**Submitting Laboratory:** London South East RGC GSTT

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