# Proposal form for the evaluation of a genetic test for NHS Service Gene Dossier/Additional Provider

**Submitting laboratory: Exeter RGC**

| |
|---|
| **1. Disorder/condition – approved name (please provide UK spelling if different from US) and symbol as published on the OMIM database** (alternative names will be listed on the UKGTN website).<br>If NGS panel test, please provide a name.<br>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. |
| Chromosome Xq26.3 Duplication Syndrome<br>(Alternative title: X-Linked Acrogigantism (XLAG)) |
| **2. OMIM number for disorder/condition**<br>If a panel test – see 1. Above. If a number of subpanels exist with different clinical entry points e.g. cancer panel test but different subpanels for different types of cancer (breast cancer, colon, phaeochromocytoma) , then please list the sub panels here: |
| 300942 |
| **3a. Disorder/condition – please provide, in laymen's terms, a brief (2-5 sentences/no more than 50 words) description of how the disorder(s) affect individuals and prognosis.** |
| X-linked Acrogigantism (X-LAG) is excessive growth that, in most cases, starts in the first few months of life and is caused by too much growth hormone (GH) being released from a tumour in the pituitary gland. Untreated patients can become very unwell due to the metabolic, cardiovascular and respiratory effects. |
| **3b. Disorder/condition – if required please expand on the description of the disorder provided in answer to Q3a.** |
| X-linked Acrogigantism (X-LAG) is a high penetrance condition (Trivellin NEJM 2014; Beckers Endo Rel Cancer 2015), resulting in early onset pituitary gigantism. If not promptly diagnosed and treated, pituitary gigantism has devastating physical and psychological consequences. X-LAG arises de novo in most cases, and only 2 familial cases have been described so far. Both pituitary hyperplasia and pituitary adenomas are found. Concomitant hyperprolactinaemia is a common finding. Resistance to somatostatin analogues is frequent, and the control of GH excess requires multi-modal treatment. |
| **4. Disorder/condition – mode of inheritance**<br>If this submission is for a panel test, please complete the mode of inheritance for each condition in the table in appendix 1. |
| X-linked; the disorder is caused by a duplication of *GPR101* that affects males and females |
| **5. Gene – approved name(s) and symbol as published on HGNC database** (alternative names will be listed on the UKGTN website)<br>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. Please provide subpanel split (described in Q2 above) in appendix 1. |
| G Protein-Coupled Receptor 10;1 *GPR101* |
| **6a. OMIM number(s) for gene(s)**<br>If a panel test – see 5. above |
| 300943 |
| **6b. HGNC number(s) for gene(s)**<br>If a panel test – see 5. above |
| 14963 |

| |
|---|
| **7a. Gene – description(s)**<br>If this submission is for a panel test, please provide total number of genes and if there are subpanels, please also list the number genes per sub panel. |
| N/A |
| **7b. Number of amplicons to provide this test (molecular) or type of test (cytogenetic)**<br>(n/a for panel tests) |
| One |
| **7c. GenU band that this test is assigned to for index case testing.**<br>**For NGS panel tests if there are sub panels, please provide GenU per subpanel.** |
| Band C |
| **8. Mutational spectrum for which you test including details of known common mutations**<br>(n/a for panel tests)<br>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 |
| Xq36 microduplication extending up to 500Kb. |
| **9a. Technical method(s) – please describe the test.** |
| Droplet digital PCR using a BioRad QX200 and TaqMan allelic discrimination probes. The assay uses one set of intragenic probes but two additional primer/probe sets are available for confirmation if required. |
| **9b. For panel tests, please specify the strategy for dealing with gaps in coverage.** |
| N/A |
| **9c. Does the test include MLPA?**<br>**(For panel tests, please provide this information in appendix 1)** |
| This is a dosage assay |
| **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?**<br>**If to be outsourced, please provide the name of the laboratory and a copy of their ISO certificate or their CPA number.** |
| In-house |
| **11. Validation process**<br><br>Please explain how this test has been validated for use in your laboratory, including calculations of the sensitivity and specificity for the types of mutations reported to cause the clinical phenotype. Note that the preferred threshold for validation and verification is ≥95% sensitivity (with 95% Confidence Intervals). Your internal validation documentation can be submitted as an appendix (and will be included in the published Gene Dossier available on the website). The validation information should include data on establishing minimum read depth and horizontal coverage for the regions of interest, reproducibility of the pipeline, accuracy of variant calling, filtering of common variants and artefacts.<br><br>If this submission is for a panel test, please provide a summary of evidence of instrument and pipeline validation and complete the tables below. |

A total of 127 patient samples were tested and 7 found to have duplications. Samples from these 7 patients were tested by arrayCGH (by the Cardiff laboratory) and the result confirmed. The Cardiff laboratory tested a subset of the cohort. One duplication that was detected by droplet digital PCR was not detected by arrayCGH, possibly due to the size of the duplication. This sample has been sent to the USA for high resolution array CGH studies and we are awaiting the results of those investigations.

**12a. Are you providing this test already?**

Yes

**12b. If yes, how many reports have you produced?**

| Droplet digital PCR Tests |
|---|
| 3 |

**12c. Number of reports with a pathogenic (or likely pathogenic) mutation identified?**

Two

**12d. Please provide the time period in which these reports have been produced and whether in a research or a full clinical diagnostic setting.**

Since July 1st 2015 (but 127 patients previously tested as part of a research study)

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

Yes.

**13b. If yes, please provide details**

Prof Marta Korbonits, Consultant Endocrinologist, Barts Hospital, is an internationally renowned expert in pituitary tumours and has collaborated with Prof Ellard's group for more than 10 years.

**14. 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.**

n/a

## EPIDEMIOLOGY

**15. Estimated prevalence and/or incidence of conditions in the general UK population**

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

**Prevalence** is total number of persons with the condition(s) in a defined population at a specific time (i.e. new and existing cases).

e.g. CF prevalence approx. 12 per 100,000 with UK population of approx. 63 million the prevalence of affected individuals in the UK is 7560

**Incidence** is total number of newly identified cases in a year in a defined population. e.g. CF incidence 1/2650 live births in a UK population with 724,000 live births in a year = 273 new cases a year

Please identify the information on which this is based.

Childhood-onset gigantism is an extremely rare disorder; no incidence data are available for the UK

**16. Estimated gene frequency** (Carrier frequency or allele frequency)

Please identify the information on which this is based.

n/a for panel tests.

Extremely low

**17. Estimated penetrance of the condition.** Please identify the information on which this is based

n/a for panel tests

Likely to be high, but limited data available

**18. Estimated prevalence of conditions in the population of people that will be tested.**

n/a for panel tests.

Expected to be high if testing is limited to individuals diagnosed with gigantism before 25 years of age.

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

**19. 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.

| | | |
|---|---|---|
| **Diagnosis** | ☒ **Yes** | ☐ **No** |
| **Treatment** | ☒ **Yes** | ☐ **No** |
| **Prognosis & management** | ☒ **Yes** | ☐ **No** |
| **Presymptomatic testing (n/a for Panel Tests)** | ☒ **Yes** | ☐ **No** |
| **Carrier testing for family members (n/a for Panel Tests)** | ☒ **Yes** | ☐ **No** |
| **Prenatal testing (n/a for Panel Tests)** | ☐ **Yes** | ☒ **No** |

# TEST CHARACTERISTICS

## 20. Analytical sensitivity and specificity

The *analytical sensitivity* of a test is the proportion of positive results correctly identified by the test (true positive/true positive + false negative). The *analytical specificity* of a test is the proportion of negative results correctly identified by the test (true negative/true negative + false positive).

This should be based on your own laboratory data for (a) the specific test being applied for or (b) the analytical sensitivity and specificity of the method/technique to be used in the case of a test yet to be set up. Please specify any types of mutations reported to cause the clinical phenotype that cannot be detected by the test.

Note that the preferred threshold is ≥95% sensitivity (with 95% Confidence Intervals).

See section 11.

## 21. 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 one year service.

For a panel test, the expected percentage diagnostic yield for the test in the target population can be presented as an alternative to clinical sensitivity and specificity?

Clinical sensitivity is likely to be high (>70%) when testing is limited to patients diagnosed before the age of 25 years. Specificity is very high.

## 22. 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**

Insufficient data available.

## 23. 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**

n/a

## CLINICAL UTILITY

**24. How will the test change the management of the patient and/or alter clinical outcome? Please summarise in 2-3 sentences – no more than 50 words.**

This test would allow to diagnose this condition thus prompting for a more adequate management of these patients.

In the presence of a positive genetic diagnosis, the use of drugs that are known to be successful in other X-LAG patients, specifically GH receptor antagonist (Trivellin NEJM 2014, Beckers ERC 2015) will be prioritised as to hopefully control the disease as quickly as possible, preventing the consequences of GH excess. This would also help in identifying the risk for future offspring to inherit the mutation and then offer appropriate counselling.

**25. Please provide full description on likely impact on management of patient and describe associated benefits for family members. If there are any cost savings AFTER the diagnosis, please detail them here.**

Therapeutic control of GPR101 requires radical surgical resection or multimodal therapy. The identification of a GPR101 duplication enables appropriate clinical management and the prevention of acromegalic features caused by excess GH. It also aids the identification of risk to offspring.

**26. If this test was not available, what would be the consequences for patients and family members? Please describe in not more than 50 of words.**

The consequence is no molecular diagnosis. The cause of this disorder was only identified in 2014 (Trivellin et al NEJM 2014) so genetic testing has not previously been available. A confirmed genetic diagnosis identifies the risk to (future) offspring.

**27. 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.

No

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

N/A

**29. 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

**30. If a panel test, is this replacing an existing panel/multi gene test and/or other tests currently carried out by your lab e.g. Noonan Spectrum Disorders 12 Gene Panel replaced multigene Sanger test for KRAS, RAF1, PTPN11 and SOS1? If so, please provide details below.**

N/A

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

None to our knowledge.

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

A 3.5 year-old female child came to medical attention because of accelerated growth (+7.79 SDS) which had started at the age of 2. Blood tests revealed extremely high GH (1620mU/l, nv <100), IGF-1 (2.17xULN) and prolactin levels (29551mU/l, nv <450).

A pituitary MRI showed a pituitary macroadenoma. A course of medical treatment (somatostatin analogues and dopamine agonists) was unsuccessful. Transcranial surgery and conventional radiotherapy did not control the disease and resulted instead in the development of permanent hypopituitarism requiring life-long steroid, thyroxine (and later in life artificially induced puberty) treatment. Finally, the control of GH excess and growth velocity was obtained by GH receptor antagonist treatment.

At the age of 12 this patient was found positive for the Xq26.3 microduplication. An earlier diagnosis, now possible for children with the same condition, would prompt the need for specific treatment and possibly avoid for these children to suffer the consequences of permanent hypopituitarism. This young girl will receive appropriate counselling when she decides to have her own family in the future.

Chromosome Xq26.3 Duplication Syndrome

# UKGTN Testing Criteria

| **Test name:**<br>**Acrogigantism (X-Linked)** | |
|---|---|
| | |
| **Approved name and symbol of disorder/condition(s):**<br>Chromosome Xq26.3 Duplication Syndrome | **OMIM number(s):**<br>300942 |
| **Approved name and symbol of gene(s):**<br>G Protein-Coupled Receptor 101 | **OMIM number(s):**<br>300943 |

| | |
|---|---|
| **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:** | |
|---|---|
| **Referrer** | **Tick if this refers to you.** |
| Consultant Clinical Geneticist | |
| Consultant Endocrinologist | |
| Consultant Paediatric Endocrinologist | |

| **Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:** | |
|---|---|
| **Criteria** | **Tick if this patient meets criteria** |
| Young-onset (diagnosed <20 years) **AND** | |
| Growth Hormone excess **AND** | |
| Increased growth velocity and/or tall stature (height SDS >2 over normal mean height or >3 over mid-parental height) | |
| **OR** At risk family members where familial mutation is known. | |

**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.**

## IS IT A REASONABLE COST TO THE PUBLIC?

**36. Based on experience what will be the national (UK wide) expected activity for requesting this test, per annum, for:**

**Index cases 10**

**Family members where mutation is known 5**

***If a NGS panel test, it is recognised that the full panel will not be used to test family members where the familial mutation is known. Please provide expected number of tests to inform completion of Q40***

**37. 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".

n/a

**38. In order to establish the potential costs/savings that could be realised in the diagnostic care pathway, please list the tests/procedures that are no longer required to make a diagnosis for index cases where index cases have a definitive molecular genetic diagnosis from the test proposed in this gene dossier.**

| | Type of test | Cost (£) |
|---|---|---|
| Imaging procedures | | |
| Laboratory pathology tests (other than molecular/cyto genetic test proposed in this Gene Dossier) | | |
| Physiological tests (e.g. ECG) | | |
| Other investigations/procedures (e.g. biopsy) | | |
| **Total cost of tests/procedures no longer required (please write n/a if the genetic test does not replace any other tests procedures in the diagnostic care pathway)** | | **n/a** |

**39. In the table below, based on the expected annual activity of index cases (Q36 above), please calculate the estimated annual savings/investments based on information provided in Q38.**

| | |
|---|---|
| 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 Q39) | (b) n/a |
| Total annual costs pre genetic test submitted for evaluation in this Gene Dossier | (a) x (b) = (c) n/a |
| Total annual costs to provide genetic test | (a) x cost of genetic testing for index case = (d) £2000 |
| Additional investment for 100% positive rate for index cases | (d) – (c) = (e) £2000 |
| Percentage of index cases estimated to be negative | (f) 30 |
| Number of index cases estimated to be negative | (f) x number of index cases = (g) 3 |
| Costs/savings to provide additional tests for index cases testing negative | (g) x (b) = (h) n/a |
| Total investment for tests for index patient activity | (e) + (h) = (i) £2000 |
| Total costs for family members | Costs for family member test x number of family members expected to test in a year (j) £1000 |
| 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) n/a |
| Total costs for family members minus any family member testing costs already provided | (j) – (k) = (l) £1000 |
| Additional costs for all activity expected in a year | (i) + (l) £3000 |

**40. Please indicate the healthcare outcomes that apply to this test after diagnosis. It is recognised that all tests recommended by the UKGTN for NHS service improve clinical management and, if a familial mutation is found, allows for prenatal testing and therefore these are not included in the list below.**

| Healthcare outcomes | Does this apply to this test? |
|---|---|
| 1. Alerts significant clinical co-morbidities | Yes |
| 2. Reduces mortality/saves lives | Yes |
| 3. Avoids irreversible harm | Yes |
| 4. Avoids diagnostic procedures/tests (some of which may be invasive) and/or multiple hospital appointments | No |
| 5. Avoids incorrect management (e.g. medication or treatment) that could be harmful | Yes |
| 6. Confirms targeted therapy/management | Yes |
| 7. Earlier diagnosis allowing commencement of treatment earlier with associated improved prognosis | Yes |
| 8. Enables access to educational and social support | Yes |
| 9. At risk family members that test negative for a familial mutation can be discharged from follow up | Yes |
| 10. At risk family members that test positive for a familial mutation have appropriate follow up | Yes |