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

| TEST – DISORDER/CONDITION – POPULATION TRIAD | | | |
|---|---|---|---|
| **Submitting laboratory:** | **Exeter RGC** | **Approved:** | **Sept 2013** |
| **1. Disorder/condition – approved name and symbol as published on the OMIM database** (alternative names will be listed on the UKGTN website) | Acrodysostosis 2, with or without hormone resistance; ACRDYS2 | | |
| **2. OMIM number for disorder/condition** | 614613 | | |
| **3a. Disorder/condition – please provide, in laymen's terms, a brief (2-5 sentences) description of how the disorder(s) affect individuals and prognosis.** | Acrodysostosis-2 is a form of skeletal dysplasia characterised by short stature, brachydactyly (shortness of fingers and toes), facial dysostosis (broad face, widely spaced eyes) and spinal stenosis. Many patients have intellectual disability and some have hormone resistance. | | |
| **3b Disorder/condition – if required please expand on the description of the disorder provided in answer to Q3a.** | | | |
| **4. Disorder/condition – mode of inheritance** | Autosomal dominant | | |
| **5. Gene – approved name(s) and symbol as published on HGNC database** (alternative names will be listed on the UKGTN website) | phosphodiesterase 4D, cAMP-specific; PDE4D | | |
| **6a. OMIM number for gene(s)**<br>**6b HGNC number for gene(s)** | 600129<br>8783 | | |
| **7a. Gene – description(s)** | chr 5q12. size: 1500Kb; 15 coding exons (15 amplicons). | | |
| **7b. Number of amplicons to provide this test (molecular) or type of test (cytogenetic)** | 15 | | |
| **7c. GenU band that this test is assigned to for index case testing** | Band E | | |
| **8. Mutational spectrum for which you test including details of known common mutations** | Missense, nonsense, splicing and small insertion/deletion mutations | | |
| **9a. Technical method(s)** | Sequencing of the entire coding region and conserved splice sites. | | |
| **9b If a panel test using NGS please state if it is a conventional panel or a targeted exome test.** | N/A | | |
| **9c. Panel/targeted exome Tests**<br>**i) Do the genes have 100% coverage? If not what is the strategy for dealing with the gaps in coverage?** | N/A | | |
| **ii) Does the test include MLPA?** | No | | |
| **iii) Does this use sanger sequencing or Next Generation Sequencing (NGS)?** | Sanger | | |

| | |
|---|---|
| **iv) If NGS is used, does the lab adhere to the 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.** | Provided by laboratory |
| **11. Validation process**<br>Please explain how this test has been validated for use in your laboratory or submit your internal validation documentation | Sequence analysis for the identification of heterozygous and homozygous mutations is employed for screening of >40 genes in the laboratory.<br>Primers were designed against reference sequence NM_001104631.1. All primers designed conform to in house criteria (which include minimum primer length, $T_m$, GC content, use of GC clamp, region of interest) and are checked for specificity and the presence of SNPs before ordering using https://ngrl.manchester.ac.uk/SNPCheckV3/snpcheck.htm. Three anonymised patient samples were used in the initial set up and optimisation of the PCR and Sanger sequencing assay. Sequencing data was checked in Mutation Surveyor against genbank files created from NM_001104631. |
| **12a. Are you providing this test already?** | ☒ **No** ☐ **Yes** |
| **12b. If yes, how many reports have you produced?**<br>**Please provide the time period in which these reports have been produced and whether in a research or a full clinical diagnostic setting.** | |
| **12c. Number of reports mutation positive** | |
| **12d. Number of reports mutation negative** | |
| **13. For how long have you been providing this service?** | N/A |
| **14a. Is there specialised local clinical/research expertise for this disorder?** | ☐ **No** ☒ **Yes** |
| **14b. If yes, please provide details** | Dr Peter Turnpenny, Consultant Clinical Geneticist, who has clinical and research interests in the genetics of skeletal disorders. |
| **15. Are you testing for other genes/disorders/conditions closely allied to this one?** Please give details | Acrodysostosis-1 caused by mutations in the cAMP binding domain of *PRKARA1* (gene dossier also submitted). This disorder is similar in phenotype to acrodysostosis-2 but usually without intellectual disability. In addition, there is phenotypic overlap between acrodysostosis and the less rare conditions, Albright Hereditary Osteodystrophy (which can include intellectual disability) and Pseudo-pseudo-hypoparathyroidism, so it is possible, or likely, that testing for some of these patients will be requested. |

| 16. Based on experience what will be the national (UK wide) activity, per annum, for: | |
|---|---|
| **16a. Index cases** | 5 referrals.<br>Acrodysostosis-2 is classified as a 'rare disease'. Since testing of acrodysostosis-1 began in November 2011 we have performed 6 diagnostic tests, 3 of which were from the UK, and we would anticipate several more referrals per year when the service is publicised further. No mutations were detected in exons 9 and 11 of *PRKARA1* in these patients, indicating the need for *PDE4D* testing (no information was received regarding hormone resistance). |
| **16b. Family members where mutation is known** | 5 |
| **17a. Does the laboratory have capacity to provide the expected national activity?** | Yes |
| **17b. If your laboratory does not have capacity to provide the full national need please could you provide information on how the national requirement may be met.**<br>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. It is appreciated that some laboratories may not be able to answer this question. If this is the case please write "unknown". | N/A |
| **18. Please justify the requirement for another laboratory to provide this test e.g. insufficient national capacity.** | N/A |

| EPIDEMIOLOGY | |
|---|---|
| **19a. Estimated prevalence of condition in the general UK population** | Unknown. Acrodysostosis-2 is rare and no accurate estimates of prevalence have been published. |
| **19b. Estimated incidence of condition in the general UK population**<br>Please identify the information on which this is based | Unknown, see above. |
| **20. Estimated gene frequency** (Carrier frequency or allele frequency)<br>Please identify the information on which this is based | Unknown. |
| **21. Estimated penetrance**<br>Please identify the information on which this is based | Up to 100%. There are 2 reports of mother—daughter pairs affected with acrodysostosis[1,2] and a report of a Japanese family with an affected mother and two siblings[3].<br>1. Hernandez *et al* 1991 Clin Genet 39: 376-382<br>2. Steinger and Pagon 1992 Clin Dysmorph 1: 201-206<br>3. Niikawa *et al 1978* Hum Genet 42: 227-232 |
| **22. Estimated prevalence of condition in the population of people that meet the Testing Criteria.** | Unknown |

## INTENDED USE

**23. 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

## 24. 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.

Sequencing: single direction sequence analysis using Mutation Surveyor software - sensitivity 99% and specificity 99% (in-house data).

## 25. 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).

In patients with radiological and clinical features of acrodysostosis, and no hormone resistance, 90-100% of patients are reported to have *PDE4D* mutations (Michot *et al* 2012, Linghart *et al* 2012). Where patients do have hormone resistance), exon 9 and 11 PRKAR1A mutations have been found in 100% of patients (Linglart *et al* 2011, 2012; Michot *et al* 2012) (see separate dossier, Acrodysostosis-1). Where hormone resistance was not specifically investigated, exon 11 *PRKAR1A* mutations were found in 40% of patients (with the remaining 60% having *PDE4D* mutations).

Linglart, *et al* 2011 NEJM 364: 2218-2226

Linglart *et al* 2012 JCEM 97: E2328-2338

Michot *et al* 2012 AJHG 90: 740-745

Lee *et al* 2012 AJHG 90: 746-751

## 26. 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).

Positive predictive value:

Lee *et al* 2012 reported that none of the *PDE4D* variants identified were observed in an internal exome dataset of 48 individuals affected by different medical conditions, or a group of 250 published exome datasets or among 5,379 exomes available from the NHLBI Exome Sequencing Project Exome Variant Server. Michot *et al* 2012 reported that all *PDE4D* variants identified were absent from control populations and from all data sets, including dbSNP129, the 1000 Genomes Project and in-house exome data.

Negative predictive value:

In a family in which a mutation has been identified the value of a negative test (for example a prenatal test) is extremely high, effectively ruling out any likelihood of the condition. However, where a diagnostic test is being performed, a negative genetic test would reduce the likelihood of the condition being present; in combining the studies of Lee *et al* (2012), Linglart *et al* (2011, 2012), and Michot *et al* (2012), 71% (24/34) of patients with radiological features of acrodystososis have exon 9 or 11 *PRKAR1A* mutations, 26% (9/34) have a mutation a second gene, *PDE4D*, and only one patient (3%) did not have a mutation in either exons 9 or 11 of *PRKAR1A* or *PDED4D*. However, as only small cohorts of patients have been screened to date it is possible that there are further susceptibility genes to be characterised.

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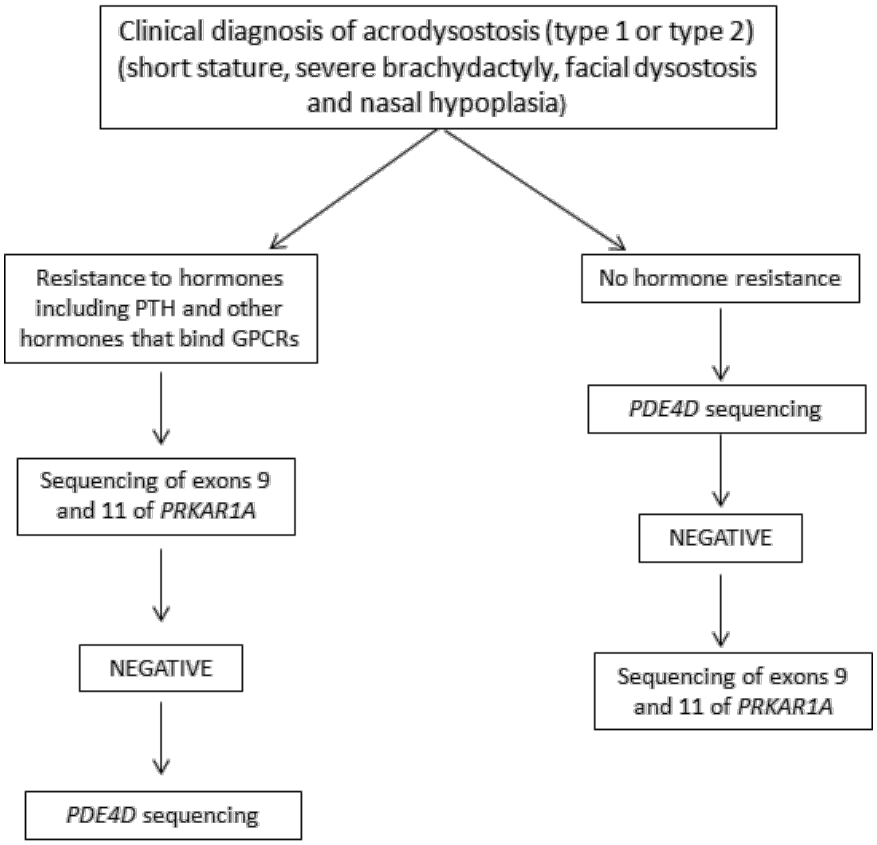
**27. Testing pathway for tests where more than one gene is to be tested**

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.




## CLINICAL UTILITY

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

Identifying a *PDE4D* mutation will confirm a diagnosis of acrodysostosis-2. The treatments for acrodysostosis are based on the symptoms that are present, ie physiotherapy for mobility problems, braces and orthodontic supports for teeth and jaw problems, and occasionally surgery to correct bone problems. Where mental retardation is present, educational and social support should be provided as necessary. This will facilitate anticipatory management and surveillance.

**29. Benefits of the test for the patient & other family members**

Please provide a summary of the overall benefits of this test.

Molecular analysis of the *PDE4D* gene in individuals with a clinical diagnosis of acrodysostosis will allow a definitive diagnosis of acrodysostosis 2 (differentiating from the possible diagnoses of Albright Hereditary Osteodystrophy and Pseudo-pseudo-hypoparathyroidism). A positive genetic test allows definitive genetic risk counselling to be offered. Those affected may request prenatal diagnosis. Prenatal diagnosis cannot be offered without a positive mutation finding.

**30. What will be the consequences for patients and family members if this test is not approved?**

If the test is not approved patients across the UK will not have equitable access to a definitive diagnosis of acrodysostosis-2. Additionally access to accurate prenatal diagnosis for those affected by acrodysostosis-2 would be difficult (see below). Early appropriate surveillance would not be put in place in a timely manner and would result in poor clinical outcomes.

**31. 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.

Clinical and radiological assessment of patient and hormone profiling can indicate a diagnosis of acrodysostosis-2. However, there are differential diagnoses of Albright Hereditary Osteodystrophy and Pseudo-pseudo-hypoparathyroidism, which can appear phenotypically very similar. Hence, molecular genetic testing provides the most powerful discriminating investigation.

For patients with acrodysostosis prenatal diagnosis can be attempted by a detailed ultrasound scan after 16 weeks. However, not all the features of acrodysostosis would be discernible, so prenatal ultrasound would not be reliable, either at 16 weeks gestation or even later. The availability of 100% reliable prenatal diagnosis by chorionic villus sampling and molecular genetic testing at 11-12 weeks gestation provides earlier resolution with diagnostic certainty, which would generally be regarded as preferable to the couple at risk.

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

None

**33. Only complete this question if there is previously approved Testing Criteria and you do not agree with it.**

Please provide revised Testing Criteria on the Testing Criteria form and explain here the changes and the reasons for the changes.

N/A

**34. List the diagnostic tests/procedures that an index case no longer needs if this genetic test is available.**

| | Type of test | Cost (£) |
|---|---|---|
| Costs and type of imaging procedures | | |
| Costs and types of laboratory pathology tests (other than molecular/cyto genetic test proposed in this gene dossier) | | |
| Costs and types of physiological tests (e.g. ECG) | | |
| Cost and types of other investigations/procedures (e.g. biopsy) | | |
| **Total cost tests/procedures no longer required** | | |
| | | |

This range of testing would have already occurred prior to arriving in clinical genetics.

**35. Based on the expected annual activity of index cases (Q15a), please calculate the estimated annual savings/investments based on information provided in Q33.**

| | |
|---|---|
| Number of index cases expected annually | |
| Cost to provide tests for index cases if the genetic test in this gene dossier was not available (see Q34) | |
| Total annual costs pre genetic test | |
| Total annual costs to provide genetic test | |
| Total savings/investment | |
| | |
| | |

**36. REAL LIFE CASE STUDY**
**In collaboration with the clinical lead, describe TWO real case examples:**

1. **prior to availability of genetic test**
2. **post availability of genetic test**

**to illustrate how the test improves patient experience and the costs involved.**

## Case example one – pre genetic test

Not available

### PRE GENETIC TEST COSTS

| | Type of test | Cost |
|---|---|---|
| Costs and type of imaging procedures | | |
| Costs and type of laboratory pathology tests | | |
| Costs and type of physiological tests (e.g. ECG) | | |
| Cost and type of other investigations/procedures (e.g. biopsy) | | |
| Cost outpatient consultations (genetics and non genetics) | | |
| **Total cost pre genetic test** | | **£** |

## Case example two – post genetic test

Not available

### POST GENETIC TEST COSTS

| | Type of test | Cost |
|---|---|---|
| Costs and type of imaging procedures | | |
| Costs and types laboratory pathology tests (other than molecular/cyto genetic proposed in this gene dosier) | | |
| Cost of genetic test proposing in this gene dossier | | |
| Costs and type of physiological tests (e.g. ECG) | | |
| Cost and type of other investigations/procedures (e.g. biopsy) | | |
| Cost outpatient consultations (genetics and non genetics) | | |
| **Total cost post genetic test** | | **£** |

**37. Estimated savings between two case examples described £**

# UKGTN Testing Criteria

| **Test name:**<br>**Acrodysostosis with or without Multiple Hormone Resistance** | |
|---|---|
| | |
| **Approved name and symbol of disorder/condition(s):**<br>Acrodysostosis 2, with or without Hormone Resistance; ACRDYS2 | **OMIM number(s):**<br>614613 |
| **Approved name and symbol of gene(s):**<br>phosphodiesterase 4D, cAMP-specific; PDE4D | **OMIM number(s):**<br>600129 |

| | |
|---|---|
| **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 | |
| | |
| | |

| **Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:** | |
|---|---|
| **Criteria** | **Tick if this patient meets criteria** |
| Clinical diagnosis of acrodysostosis (short stature, severe brachydactyly, facial dysostosis, and nasal hypoplasia) **OR** | |
| PRKAR1A negative | |
| 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.**