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

Submitting laboratory: Edinburgh 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).
If NGS panel test, please provide a name.

If this submission is for a panel test please complete the Excel spread sheet, Appendix 1, available for download from the UKGTN website, and list all of the conditions grouped by sub panels if applicable.

Microcephalic Osteodysplastic Primordial Dwarfism, Type II; MOPD2

2. OMIM number for disorder/condition

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 – providing name of each sub panel.

210720

3a. Disorder/condition – to help commissioners to understand the impact of this condition please provide, in laymen's terms (e.g tubes in the kidney (renal tubule) or low sugar in the blood (hypoglycaemia)), a brief (2-5 sentences/no more than 50 words) description of how the disorder(s) affect individuals and prognosis.

Microcephalic osteodysplastic primordial dwarfism type II (MOPDII) is a disorder of extreme growth failure, which starts before birth. Growth delay continues after birth, leading to severe proportionate short stature (final adult height is ~3 feet) and a small head (Willems et al., 2010). Patients often have normal intelligence or mild learning difficulties. All MOPDII patients have *PCNT* mutations.

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

Patients with MOPDII are at risk of additional complications such as diabetes and brain aneurysms. A genetic diagnosis of MOPDII can therefore allow for correct clinical management of these patients, including regular monitoring for signs of insulin resistance and blood vessel abnormalities.

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 the Excel spread sheet, Appendix 1, available for download from the UKGTN website, and list all of the genes grouped by sub panels if applicable.

Pericentrin (*PCNT*)

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

If a panel test – see 5. above

605925

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

If a panel test – see 5. above

16068

7a. Gene – description(s)

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.

PCNT is a component of the pericentriolar material (PCM) and is critical in the normal function of centrosome biogenesis (Luo and Lelletier, 2014). Loss of PCNT leads to the reduction of astral microtubules, altering the position of the mitotic spindle apparatus. As a result there is asymmetrical cell division, reduced cell proliferation and thus a global decrease in cell number that results in global growth failure.

7b. Number of amplicons to provide this test (molecular) or type of test (cytogenetic)

(n/a for panel tests)

51 amplicons

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

For NGS panel tests if there are sub panels, please provide GenU per subpanel.

GenU band G

8. Mutational spectrum for which you test including details of known common mutations

(n/a for panel tests)

Nonsense, missense, small insertions, deletions and splicing variants. All variants reported to date, result in premature termination of the open reading frame.

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

Bidirectional fluorescent sequencing

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.

Provided by lab

11. Validation process

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.
If this submission is for a panel test, please provide a summary of evidence of instrument and pipeline validation and complete the tables below.

Bidirectional fluorescent sequencing is used routinely by the lab for mutation scanning of many genes. Prior to use all, primers were checked for SNPs and one normal control was sequenced to confirm specific amplification. Confirmation of known mutations in positive controls from Prof. Jackson's research group was also carried out.

12a. Are you providing this test already?
No
12b. If yes, how many reports have you produced?
N/A
12c. Number of reports with a pathogenic (or likely pathogenic) mutation identified?
N/A
12d. Please provide the time period in which these reports have been produced and whether in a research or a full clinical diagnostic setting.
N/A
13a. Is there specialised local clinical/research expertise for this disorder?
Yes
13b. If yes, please provide details
Prof. Andrew Jackson has a research group at the Institute of Genetic and Molecular Medicine. They have been studying genes associated with primordial dwarfism and microcephaly. This test is has been offered by Prof. Jackson's laboratory, on a research basis, since 2008.
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.

Estimated prevalence: ≤100 affected individuals in UK. Estimated incidence: 2-3 new cases per year.

Estimates are based on clinical experience as national/international expert and contact with patient groups.

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

Please identify the information on which this is based.

n/a for panel tests.

Allele frequency <1:700, based on the estimated prevalence stated above.

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

n/a for panel tests

Fully penetrant. Carriers do not have a phenotype.

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

n/a for panel tests.

Unknown

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).

Approximately 99% for detecting base changes, small deletions and insertions and splice site mutations. One exon-scale deletion has been reported in the literature (Rauch et al. 2008). This would be detected in homozygous individuals, as no PCR product would be generated. However it would not be detected if patients were heterozygous.

If there is a strong suspicion for a deletion, or it becomes apparent that deletions make up a substantial mutational load for the gene, we could design and carry out a bespoke ddPCR or carry out a long range PCR of the intron to look for breakpoints, and could design a bespoke MLPA assay using the MRCHolland design guidelines.

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 = 95%

A second cryptic mutation has not been identified. A few cases have been found by research testing to have one sequence variant. However subsequent functional analysis (cellular immunofluorescence) has demonstrated PCNT to be absent.

Clinical specificity= >99.9%

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

Positive predictive value= ~100%

Negative predictive value= 95%

MOPDII is a homogenous disorder caused by *PCNT* mutations. If no pathogenic *PCNT* mutations have been identified then the patient does not have MOPDII, but another form of primordial dwarfism. Apart from a small percentage who may have a cryptic mutation that cannot be identified. Patients with a positive result will have MOPDII.

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.

There are significant comorbidities associated with MOPDII, including severe insulin resistance (approximately 50% are diabetic) and cerebrovascular disease such as Moyamoya disease and aneurysms (>50%). Confirming a diagnosis of MOPDII, by genetic testing of *PCNT*, will allow patients to receive appropriate surveillance and earlier management for complications. Excluding sequence variants in *PCNT* is helpful to support decisions not to perform regular MRI screening.

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.

Finding a mutation confirms the mode of inheritance as autosomal recessive and allows carrier testing in other family members and appropriate counselling. Prenatal diagnosis would be available to couples who are both identified carriers.

26a. 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.

Diagnosis would not be made and the disease may not be managed correctly. Further invasive testing may be carried out. Further affected children could be born (recurrence risk is 1 in 4 if both parents are carriers).

26b. The consequences for patients and family members if this test was not available – if required please expand on the response provided in question 26a.

N/A

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.

Testing for absence of PCNT in patient cells (e.g. fibroblasts) is possible, but this is more invasive and costly and is not feasible for a routine molecular diagnostic lab.

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.

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

X was given a clinical diagnosis of MOPD II. This led to considerable parental anxiety and 18 monthly neuroimaging under general anaesthetic. *PCNT* sequencing did not identify sequence variants and the diagnosis was revised to a non-syndromic form of primordial dwarfism. Further neuroradiological investigation and monitoring for diabetes have ceased.

TESTING CRITERIA

33. Are previously approved Testing Criteria available that define the clinical entry point for this test?

No

34. If there is previously approved Testing Criteria that you agree to, please list below and transcribe in to this submission. If for NGS sub panels please state the sub panel that the Testing Criteria is to be used for.

N/A

35.

If there is previously approved Testing Criteria that you do not agree to, please submit revised Testing Criteria in this Gene Dossier and list below where the Testing Criteria replaces current criteria.

N/A

UKGTN Testing Criteria

Test name: **Microcephalic Osteodysplastic Primordial Dwarfism, Type II**	
Approved name and symbol of disorder/condition(s): Microcephalic Osteodysplastic Primordial Dwarfism, Type II; MOPD II	**OMIM number(s):** 210720
Approved name and symbol of gene(s): Pericentrin; PCNT	**OMIM number(s):** 605925

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 Paediatric Neurologist	
Consultant Paediatric Endocrinologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Postnatal height: -5 SD below the mean or smaller **AND**	
OFC (occipitofrontal circumference): -5 SD below the mean or smaller **AND**	
At birth, small for gestational age	
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.

Approval date: March 2017

Submitting laboratory: Edinburgh RGC

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: <20 per annum (approximately 1-2 new cases per month)

Family members where mutation is known: <40 per annum

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

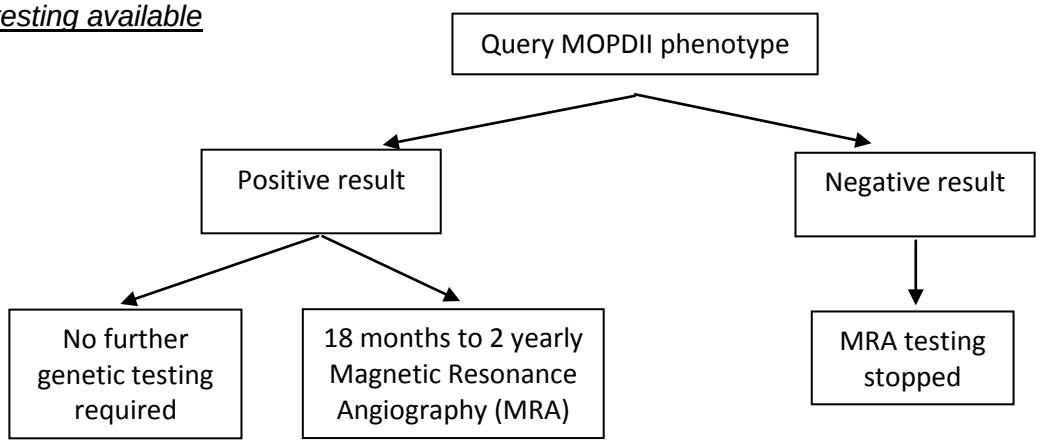
38. In order to establish the potential costs/savings that could be realised in the diagnostic care pathway, please list the tests/procedures that are no longer required to make a diagnosis for index cases where index cases would have the molecular genetic test proposed in this gene dossier at an earlier stage in the pathway. It is the tests/procedures that would be stopped for patients that are eligible for the gene test.

This information will be used to calculate the overall investment / savings required in Q39

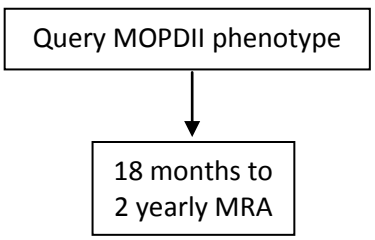
Example: The introduction of a 95 gene panel for syndromic and non syndromic hearing loss would allow those patients who are recognised early enough in their pathway to diagnosis to be offered the genetic test instead of having sequential gene tests for individual genes already available and repeated ECGs, ERGs & renal ultrasounds as part of the diagnostic pathway although these may still be required as part of management after diagnosis.

The introduction of *PCNT* testing will allow detection of patients at risk of neurovascular complications (MOPD II), with negative testing meaning that 18 months to 2 yearly Magnetic Resonance Angiography will not be required, as per the flow diagrams below.

PCNT testing available



PCNT testing is **not** available



	Type of test	Cost (£)
Imaging procedures	MR Angiography scan	£1298
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)		
Associated inpatient stays in the diagnostic pathway		
Total cost of tests/procedures to be stopped (please write n/a if the genetic test does not replace any other tests procedures in the diagnostic care pathway)		£1298 (If *PCNT* testing was negative)
If any of the tests/procedures listed above would be carried out on individuals after having the genetic test because the genetic test did not pick up a pathogenic mutation (i.e. negatives), please indicate the costs for these tests to continue to diagnosis. *For example a panel test replaces single gene tests that have been included above, but after the panel test an individual that tests negative would not need to have these single gene tests, because the genes were on the NGS panel.*		

39. Please complete the Excel spread sheet available to download from the UKGTN website to calculate the estimated investment or savings, based on the expected annual activity of index & family cases (Q36 above) and using the information provided in Q38.

Number of index cases expected annually	20
Number of family member tests expected annually	40
Cost to provide index case test	£400
Cost to provide family member test	£140
Costs associated with tests/procedures for index cases if the genetic test in this Gene Dossier was not available	£1,298
Costs associated with tests/procedures for index cases that test negative for the genetic test in this Gene Dossier	£0
Total annual costs for diagnostic tests prior to introduction of the genetic test submitted for evaluation in this Gene Dossier	£25,960
Total annual costs to provide genetic test	£8,000
Additional savings or investment for 100% pick up rate for index cases	-£17,960
Percentage of index cases expected not to find a pathogenic mutation (negatives)	83%
Number of index cases estimated to not find a pathogenic mutation (negatives)	16.6
Costs or savings to provide additional tests for index cases that test negative	£0
Total savings / investment prior to application of marginal reduction if applicable	-£17,960
If a panel test and there are genes on the panel test that are already available on either other panel tests or single gene tests please estimate/suggest a marginal percentage reduction of the investment/savings. If you feel this is NOT applicable please leave this as 0%.	0%
Marginal percentage reduction if applicable applied to the savings/investment	£0
TOTAL SAVINGS / INVESTMENT for tests for INDEX CASES	**-£17,960**
Total costs for family members	£5,600
If family testing is already available for any of the genes on this panel across the Network, please estimate the associated funding for these tests.	£0
TOTAL SAVINGS / INVESTMENT for tests for FAMILY MEMBERS	£5,600
ADDITIONAL INVESTMENT / SAVINGS FOR ALL ACTIVITY EXPECTED PER ANNUM	-£12,360

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	No
4. Avoids diagnostic procedures/tests (some of which may be invasive) and/or multiple hospital appointments	Yes
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	No
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