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

Submitting laboratory: Leeds 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 appendix 1 listing all of the conditions included using approved OMIM name, symbol and OMIM number.

Autosomal Recessive Primary Hypertrophic Osteoarthropathy (PHOAR) Panel

(See appendix 1)

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:

See appendix 1

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.

Hypertrophic osteoarthropathy is a syndrome characterized by skin thickening, sweating, increase in the soft tissue around the end of the fingers and toes (digital clubbing) and excessive bone formation of the long bones and painful joint swelling (periostosis). It may be complicated by bone marrow failure (presenting as anaemia) due to the progressive replacement of normal (functional) bone marrow with fibrous (non-functional) tissue (myelofibrosis).

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

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. Please provide subpanel split (described in Q2 above) in appendix 1.

Hydroxyprostaglandin Dehydrogenase 15-(NAD); HPGD

Solute Carrier Organic Anion Transporter Family Member 2A1; SLCO2A1

6a. OMIM number(s) for gene(s)
If a panel test – see 5. above

HPGD: 60168
SLCO2A1: 601460

6b. HGNC number(s) for gene(s)
If a panel test – see 5. above

HPGD: 5154

SLCO2A1: 10955

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.

2 genes (HPGD and SLCO2A1)

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

n/a

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.

Band G (1-50 genes analysed by NGS)

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

n/a

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

Target enrichment is performed using an Agilent SureSelect CustomXT hybridisation-based DNA bait library designed by ourselves. Library preparation is performed using Agilent SureSelect reagents and a derivation of the manufacturer's protocol. Sequencing is performed on the Illumina HiSeq.

Data is processed through an in-house bioinformatics pipeline – alignment (BWA), variant calling (GATKLite) and variant annotation (Alamut Batch).

Coverage of regions of interest (coding regions for all genes +/- 20 nucleotides) is assessed using an in-house spreadsheet.

Variants are filtered using an automatic algorithm which removes likely-benign variants based on dbSNP minor allele frequency and location (within gene regions of interest, as described above). Remaining variants are assessed manually by two scientists using the standard 5-class system, as per ACGS Best-Practice Guidelines. Variants considered of clinical utility (class 4 and 5) are confirmed by dideoxy sequencing, with primers designed in-house, before communicating the findings to the referrer in a fully interpretive report.

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

Gaps in coverage are filled by dideoxy sequencing or (on a case-by-case basis) stated as incomplete coverage on the report.

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

No, however, dosage analysis using comparative depth of coverage of NGS data is included.

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

Yes

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 the 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.

Instrument (HiSeq2000) and bioinformatics pipeline was validated on equivalent panel chemistry (hereditary cancer genes panel), enabling a comparison to be made against sensitivity of existing pipelines (Sanger sequence analysis and NGS analysis based on enrichment by long range PCR). 100% concordance was recorded for 480 variants (101 unique) between the panel test and gold-standard PCR-based analysis.

Specific validation of this reagent ("Selected Genes" panel) took place on 49 unique variants, again with 100% concordance. No false positives or false negatives (following manual scrutiny & analysis of data) were indicated during the validation process; (105 tested samples, 150 analysed unique variants, no incorrect calls [false-positive or false-negative] = 98% accuracy at 95% CI). Independent validation of PHOAR panel specifically has not taken place, as this is a very rare disease service.

Post-validation, a single false-negative result was identified in a different panel using the same chemistry and analytical pipeline; this involved a single-base substitution at the final base of a long (27 base) mononucleotide repeat tract. This result was replicated. We have inferred from this that sensitivity is reduced within or adjacent to mononucleotide repeat regions; a subsequent review of all HPGD and SLCO2A1 variants listed in the "HGMD Professional 2015.2" database indicated no cases of reported variants in such regions in these genes. The overall reduction in sensitivity due to this issue cannot be quantified as insufficient unique variant controls are available.

Minimum read depth is set at 30X (15X for intronic regions); this was the cut-off used in establishing the sensitivity and specificity of the technique, and reflects standard practice in other diagnostic services in our laboratory. Horizontal coverage is defined as all coding regions for the reported transcripts plus 20 nucleotides of flanking non-coding sequence. Independent assessment of 8 sequenced samples indicated 100% coverage at 30X for the entire region of interest.

Annotated variants are filtered to include those from selected (relevant) reference sequences only and to exclude variants with a dbSNP minor allele frequencies ("rsMAF"; derived from the 1000 Genomes project) >5%. Internal validation indicated that, for 63 coding variants with rsMAF >2% in a range of genes tested in our laboratory, all variants had been independently (i.e. in a prior variant classification exercise) classified as "benign" (class 1). We are aware of no diagnostically relevant variants in either of the genes on this panel with MAF >5%.

For panel tests:

WHOLE PIPELINE:

Sensitivity 98% (95% CI)

Read depth minimum cut off: 30X (15X for intronic regions).

	Previously tested	NGS test concordant results	NGS False negative
Number of patient samples	**105**	**N/A**	**N/A**
Unique variants (total)	**150**	**150**	**0**
SNV	**138**	**138**	**0**
Indel (1bp to X bp)	**12**	**12**	**0**
CNV*	**34**	**34**	**0**

Specificity 98% (95% CI)

	Variant confirmed by other method	NGS False positive
Number of patient samples with a variant detected by NGS	**105**	**0**
Unique variants (total)	**150**	**0**
SNV	**138**	**0**
Indel (1bp to X bp)	**12**	**0**
CNV*	**34**	**0**

SPECIFIC PANEL (Selected Genes):

Sensitivity 94% (95% CI)

Read depth minimum cut off: 30X (15X for intronic regions).

	Previously tested	NGS test concordant results	NGS False negative
Number of patient samples	**8**	**N/A**	**N/A**
Unique variants (total)	**49**	**49**	**0**
SNV	**46**	**46**	**0**
Indel (1bp to X bp)	**3**	**3**	**0**
CNV*	**1**	**1**	**0**

Specificity 94% (95% CI)

	Variant confirmed by other method	NGS False positive
Number of patient samples with a variant detected by NGS	**8**	**0**
Unique variants (total)	**50**	**0**
SNV	**46**	**0**
Indel (1bp to X bp)	**3**	**0**
CNV*	**1**	**0**

*CNV assessed subsequently on different cohort of patients and therefore not included in the numbers of unique variants (total) given in the above tables. Sensitivity and specificity figures are calculated for sequence variants (SNV and indels) only.

Note: **specificity** of the panel test for clinically actionable variants (class 4 and 5 variants) is anticipated to be 100%, as all such findings are confirmed by an independent method (e.g. dideoxy sequencing) prior to clinical reporting. In practice, the rates of artefactual variant calls in NGS data are much higher, however, these are not reported, and are filtered by automatic and/or manual protocols resulting in no false positives being scored/reported clinically.

12a. Are you providing this test already?

Yes

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

Sanger Based Tests	NGS Based Tests
16	2

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

Sanger Based Tests	NGS Based Tests
8	1

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

September 2010 to July 2015. All produced within a full diagnostic setting

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

Yes

13b. If yes, please provide details

Prof. David Bonthron, Clinical Professor of Genetics, leads the Molecular Genetics Research Group within the Leeds Institute of Biomedical & Clinical Sciences of the Faculty of Medicine and Health at the University of Leeds. His group identified and published both HPGD and SLCO2A1 genes as causes of PHO (see Uppal et al (2008) Mutations in 15-hydroxyprostaglandin dehydrogenase cause primary hypertrophic osteoarthropathy. Nat. Genet. 40(6): 789-793; Diggle et al (2010) Common and recurrent HPGD mutations in Caucasian individuals with primary hypertrophic osteoarthropathy. Rheumatology (Oxford) 49(6): 1056-1062 and Diggle et al (2012) Prostaglandin Transporter Mutations Cause Pachydermoperiostosis with Myelofibrosis. Hum Mutat. 33(8): 1175–1181.)

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.

The prevalence of PHO in the general UK population is unknown. It is rare but of increased prevalence within consanguineous communities.

According to Orphanet "Prevalence and incidence of rare diseases: Bibliographic data" (Number 1: July 2015) there have been 204 cases of pachydermoperiostosis (PDP; a form of primary hypertrophic osteoarthropathy) reported in the literature worldwide.

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

Please identify the information on which this is based.

n/a for panel tests.

n/a

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

n/a for panel tests

n/a

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

n/a for panel tests.

n/a

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).

For panel tests please re-state the analytical sensitivity and specificity for the data provided in Q11. Please also detail any mutation types not detected by the assay.

The instrument (HiSeq2000) and bioinformatics pipeline, using an equivalent panel chemistry (hereditary cancer genes panel), has been shown to have a sensitivity of 98% (95% CI) and specificity of 98% (95% CI). The specific reagent used for this panel has been shown to have a sensitivity of 94% (95% CI) and specificity of 94% (95% CI). These reductions are only due to fewer numbers of unique known variants that were analysed during validation of this reagent and there have been no results to suggest that it would not meet the same level (98%) of sensitivity and specificity as the equivalent reagent.

This testing strategy will not detect intronic or regulatory variants that are outside of the coding regions +/-20bp.

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?

Previous analysis of patients referred for HPGD gene testing only by Sanger sequencing (September 2010 to November 2014) resulted in a diagnostic yield of 50% and it is envisaged that the additional analysis of SLCO2A1 will increase this yield. (In a study of clinically typical PHO patients who were HPGD mutation-negative, biallelic SLCO2A1 mutations were found in 12 out of 13 cases; Diggle et al. 2012.)

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

n/a

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.

Avoidance of invasive investigation of signs and symptoms (which mimic those of hypertrophic osteoarthropathy secondary to malignancy). Risk of myelofibrosis is specifically associated with SLCO2A1 mutation.

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.

Patients with a positive diagnosis of HPGD- or SLCO2A1-related PHOAR can be spared the need for protracted, expensive and even invasive tests aimed at identifying an occult pathology associated with a secondary form of hypertrophic osteoarthropathy. These patients may also benefit from pharmacological interventions to reduce prostaglandin levels and alleviate symptoms. The identification of biallelic SLCO2A1 mutation(s) will also enable the identification of patients at risk (or in the early stages) of myelofibrosis.

The associated benefits of the genetic diagnosis to the wider family not only include the empowerment of knowing the cause of the condition but also provision of information regarding recurrence risks and importantly the opportunity to ascertain sub-clinically affected relatives (particularly female relatives who tend to present with milder manifestations, which is hypothesised to be due to the lower prostaglandin levels in females) who may then benefit from early clinical and therapeutic interventions.

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.

Undiagnosed patients may undergo long series of investigations to look for suspected malignancy (especially lung cancer).

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.

Measurement of urine or plasma prostaglandin and metabolites can confirm the diagnosis. This is not widely available and normal reference ranges are not known.

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.

Biallelic SLCO2A1 mutation is associated with a risk of ~50% (or greater) of myelofibrosis, which merits haematological investigation, monitoring and possibly treatment.

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.

Autosomal recessive primary hypertrophic osteoarthropathy 2 gene panel replaces Sanger sequencing test for HPGD mutations.

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

n/a

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

A local consanguineous family of Northern Pakistani origin had two siblings affected with primary hypertrophic osteoarthropathy. This family was included in the research cohort that helped to identify HPGD mutations as a cause of PHOAR (Family B in Uppal et al (2008)

Mutations in 15-hydroxyprostaglandin dehydrogenase cause primary hypertrophic osteoarthropathy. Nat. Genet. 40(6): 789-793). The affected children were found to be homozygous for the HPGD missense mutation c.418G>C p.(Ala140Pro).

Identification of this mutation and confirmation of the parental carrier status enabled testing to be offered to other appropriate relatives, including carrier testing of aunts and uncles. This carrier testing identified another couple (maternal aunt married to paternal uncle) who were both heterozygous carriers of the familial mutation.

This couple were pregnant at the time of carrier testing and the information gained from the genetic testing gave the opportunity for the baby (at 1 in 4 risk of being affected) to be tested at birth using a cord blood sample. In this case the baby was found to not carry the familial mutation and therefore was highly unlikely to be affected with PHO, providing reassurance to the family. If the baby had been found to be affected this early diagnosis, prior to the onset of clinical features, would have enabled early intervention with targeted therapeutic measures, such as non-steroidal anti-inflammatory drugs.

UKGTN Testing Criteria

Test name: Autosomal Recessive Primary Hypertrophic Osteoarthropathy (PHOAR) 2 Gene Panel	
Approved name and symbol of disorder/condition(s): See website listing	**OMIM number(s):**
Approved name and symbol of gene(s): See website listing	**OMIM number(s):**

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 Rheumatologist	
Consultant Adult Rheumatologist	
Consultant Paediatric Dermatologist	
Consultant Adult Dermatologist	
Consultant Adult Respiratory Physician	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Unexplained digital clubbing **AND** one of the following:	
• Periostosis	
• Pachydermia	

Additional Information:

For panel tests:
At risk family members where familial mutation is known do not require a full panel test but should be offered analysis of the known mutation.

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 2

Family members where mutation is known 4

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".

Laboratory has capacity to provide service for the full national need.

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.

Undiagnosed patients may undergo long series of investigations of signs and symptoms (which mimic those of hypertrophic osteoarthropathy secondary to malignancy, particularly lung cancer). The exact extent of testing that is currently performed and could be avoided is difficult to accurately capture and it is not possible to reflect the cost of repeat clinic appointments and referrals to different departments and specialties for investigation.

	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)		

39. In the table over leaf, 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) **2**
Cost to provide tests for index cases if the genetic test in this Gene Dossier was not available (see Q39)	(b) **£0**
Total annual costs pre genetic test submitted for evaluation in this Gene Dossier	(a) **2** x (b) **£0** = (c) **£0**
Total annual costs to provide genetic test	(a) **2** x (cost of genetic testing for index case) **£610** = (d) **£1220**
Additional investment for 100% positive rate for index cases	(d) **£1220** – (c) **£0** = (e) **£1220 investment**
Percentage of index cases estimated to be negative	(f) **50%**
Number of index cases estimated to be negative	(f) **0.5** x number of index cases **2** = (g) **1**
Costs/savings to provide additional tests for index cases testing negative	(g) **1** x (b) **£0** = (h) **£0**
Total savings/investment for tests for index patient activity	(e) **£1220** + (h) **£0** = (i) **£1220**
Total costs for family members	Costs for family member test **£195*** x number of family members expected to test in a year **4** = (j) **£780** (*average of 170 and 220 cost depending on number of amplicons required for family test.)
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 **0** x estimated number of tests for family members already provided **4** = (k) **0**
Total costs for family members minus any family member testing costs already provided	(j) **£780** – (k) **0** = (l) **£780**
Additional costs for all activity expected in a year	(i) **£1220** + (l) **£780** = **£2000**

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	No
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	Yes
8. Enables access to educational and social support	No
9. At risk family members that test negative for a familial mutation can be discharged from follow up	No
10. At risk family members that test positive for a familial mutation have appropriate follow up	Yes

Appendix 1

Genes in panel test and associated conditions

OMIM standard name of condition (please provide the conditions that the test is for which may NOT necssarily be the condition that is linked to the gene on OMIM)	OMIM symbol of condition	OMIM number of condition	Mode of inheritance	HGNC standard name of gene	HGNC symbol of the gene	HGNC number of the gene	OMIM number of the gene	Evidence of association between gene and condition	% of horizontal coverage of gene	MLPA
HYPERTROPHIC OSTEOARTHROPATHY, PRIMARY, AUTOSOMAL RECESSIVE, 1	PHOAR1	259100	Autosomal recessive	HYDROXYPROSTAGLANDIN DEHYDROGENASE 15-(NAD)	HPGD	5154	601688	Uppal *et al* (2008). Mutations in 15-hydroxyprostaglandin dehydrogenase cause primary hypertrophic osteoarthropathy. Nat. Genet. 40(6): 789-793. Diggle *et al* (2010). Common and recurrent HPGD mutations in Caucasian individuals with primary hypertrophic osteoarthropathy. Rheumatology (Oxford) 49(6): 1056-1062.	100% coverage of coding sequence +/-20bp of flanking intronic/ UTR sequence.	No, however, dosage analysis using comparative depth of coverage of NGS data is included.
HYPERTROPHIC OSTEOARTHROPATHY, PRIMARY, AUTOSOMAL RECESSIVE, 2	PHOAR2	614441	Autosomal recessive	SOLUTE CARRIER ORGANIC ANION TRANSPORTER FAMILY, MEMBER 2A1	SLCO2A1	10955	601460	Diggle *et al* (2012). Prostaglandin Transporter Mutations Cause Pachydermoperiostosis with Myelofibrosis. Hum Mutat. 33(8): 1175–1181.	100% coverage of coding sequence +/-20bp of flanking intronic/ UTR sequence.	No, however, dosage analysis using comparative depth of coverage of NGS data is included.