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

Submitting laboratory:
London North East RGC GOSH

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.

Renal Tubulopathy 37 Gene Panel (consisting of 9 tests)

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 table in 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.

The renal tubule is responsible for maintenance of acid-base balance, blood pressure and the correct concentration of electrolyte in the body. Consequently, disorders in renal tubular function are typically associated with abnormalities in these critical physiological parameters. Depending on the severity of the disorder, these abnormalities can be life-threatening and/or associated with severe complications, including sudden death, prematurity, critically high or low blood pressure, heart arrhythmia, failure-to-thrive and kidney stones, or only manifest in mild abnormalities seen on blood tests.

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

See table in appendix 1

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.

See table in appendix 1

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.

See table in appendix 1

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

See table in appendix 1

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

See table in appendix 1

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.
37 genes are being tested
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 Magnesium Related Renal Tubulopathy 10 gene panel GenU band G Dent Disease 2 gene panel GenU band G Hypokalaemic Alkalosis 8 gene panel GenU band G Hyperkalaemic Acidosis 8 gene panel GenU band G Hypophosphatemia with Hypercalciuria 3 gene panel GenU band G Autosomal Dominant Interstitial Kidney Disease 2 gene panel GenU band G Nephrogenic Diabetes Insipidus 2 gene panel GenU band G Calcium Related Renal Tubulopathy 3 gene panel GenU band G Renal Tubular Acidosis 4 gene panel GenU band G
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.
Multiplex PCR (Multiplicom TUBMASTR kit), followed by NGS (MiSeq)
9b. For panel tests, please specify the strategy for dealing with gaps in coverage.
Pilot testing in more than 80 patients has shown >30x coverage in >98% of amplicons. Only 2 regions of high GC content were problematic. These will be covered by Sanger sequencing if indicated.
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?
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.

For panel tests:

This test utilises an off-the-shelf library preparation kit (Multiplicom TUBMASTR™). Bioinformatic analysis restricts variant calling to genes in this panel, as detailed elsewhere in this dossier.

Analysis of data from the MiSeq/HiSeq sequencing instruments is conducted using an in-house developed pipeline of open-source tools, providing read alignment (BWA; Burrows Wheeler Aligner v0.6.1-r104: http://bio-bwa.sourceforge.net/), pileup (SamTools; Samtools v0.1.18: http://samtools.sourceforge.net/), variant calling (VarScan2; VarScan2 v2.3.6: http://varscan.sourceforge.net/) and variant annotation (VEP; Variant effect predictor v73: http://www.ensembl.org/info/docs/tools/vep/index.html). Pipeline output is limited to variants within 14 base pairs of the acceptor splice site and 6 base pairs of the donor splice site of coding exons. Variants must be present in 20% of at least 30 reads to be called. Further filtering excludes variants present at 2% or greater in exome variant server (EVS) or 1000 genomes datasets or in greater than three patients on a run of 16.

The combination of Multiplicom library preparation with Illumina sequencing, analysed with the in-house data analysis pipeline, has been validated using SNVs and small indels (1-10bp) detected by Sanger sequencing or by alternative NGS technology (n=683). In addition, ten positive control samples were run for validation and verification for this panel. All mutations were detected using the standard analysis pipeline. The standard pipeline is not configured to detect exon-level deletions and duplications therefore no CNVs were included. These figures have been included in the validation data below.

Samples will routinely be checked for CNVs using ExomeDepth (http://cran.r-project.org/web/packages/ExomeDepth/index.html)and positives confirmed by qPCR or MLPA if available, however, the number of positive controls available to the laboratory is insufficient to conclude that this method will robustly detect all CNVs. Mutation negative reports will therefore not state that CNVs have been excluded.

For panel tests:

Sensitivity 97.3% (95% CI)

Read depth minimum cut off: 30

	Previously tested	**NGS test concordant results**	**NGS False negative**
Number of patient samples	**88**	**88**	**0**
Unique variants (total)	**111**	**111**	**0**
SNV	**94**	**94**	**0**
Indel (1bp to 10 bp)	**16**	**16**	**0**
CNV	**0**	**0**	**0**

If a reference sample (eg HapMap/CEPH DNA) has been tested please complete this table too:

	Known variants	**NGS test concordant results**	**NGS False negative**
Reference sample details			
Unique variants (total)			
SNV			
Indel (1bp to X bp)			
CNV			

Specificity X% (X% CI)

Specificity figures are not listed, since all reported variants are confirmed by Sanger sequencing or qPCR/MLPA. Therefore the combined specificity for reported variants of both tests will be approaching 100%.

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

12a. Are you providing this test already?

Yes

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

Sanger Based Tests	NGS Based Tests
2	65

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

Sanger Based Tests	NGS Based Tests
2	57

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

Reports have been produced in a clinical diagnostic setting from 09/2014 to 07/2015

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

Yes

13b. If yes, please provide details

Great Ormond Street Hospital hosts a large specialised clinic for tubulopathies, caring for more than 200 patients. This is the only such clinic for affected children in the country. The physicians involved, Drs Van't Hoff, Kleta and Bockenhauer are internationally recognised experts for tubulopathies

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 tested disorders are all considered rare disorders using the definition of <1:2000. Precise epidemiological data for these rare diseases are not available, but estimated incidence is <1:100.000 for most of the included disorders. Thus, the combined incidence of the 13 tested disorders is likely around 1:10.000

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.

Based on the validation data the analytical sensitivity is 97.3% (95% CI) and the specificity is approaching 100%. The standard NGS pipeline is not configured to detect large CNVs, but we will attempt to detect these using the Exome depth software. Homozygous CNVs will be detected due to the absence of NGS reads (several have already been detected in our pilot data).

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?

Based on our pilot data, clinical sensitivity is >85%. In the first 65 patients, mutations have been identified in 57. Sensitivity obviously depends on the accuracy of the clinical phenotype of patients referred for testing. Specificity is expected to be 100%, although we do not intend to offer this test to patients who have not been clinically evaluated and thought to have a tubulopathy.

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.

1. Awareness of and consequent screening for potential complications, such as a) renal stone disease, b) hearing problems, c) dehydration
2. Initiation of proper treatment in at risk patients prior to development of symptoms.

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.

Provision of a molecular diagnosis provides a clear explanation for the disease and allows screening of family members at risk, as well as prenatal screening. Identification and prevention of complications, such as renal stones will save costly treatment for obstructive stone disease and prevent the often associated deterioration in kidney function.

Some of the disorders, e.g. Nephrogenic diabetes insipidus are associated with recurrent dehydration and consequent brain damage if not adequately treated. Distal renal tubular acidosis is associated with recurrent urolithiasis and loss of kidney function, if not adequately treated. Pre- or postnatal screening of at risk patients allows commencement of adequate treatment to prevent these complications.

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.

Uncertainty with regards to cause of the patients problems and the adequacy of treatment.

Inability to commence adequate treatment in at risk patients without extensive clinical investigations.

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.

All tested disorders are associated with specific biochemical abnormalities. Some of these need hospitalisation (e.g. DDAVP test, acid-loading test), are difficult, especially in very young children, and results are often equivocal. Molecular testing can avoid these tests in at risk persons and provide certainty of the diagnosis.

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.

Mutations in the following genes are associated with symptoms unrelated to the phenotype:

KCNA1 (episodic ataxia/myokymia)

SLC4A1 (ovalocytosis)

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

We would discuss such findings with the referring clinician prior to reporting. If the clinician is not a clinical geneticist then a referral to / discussion with clinical genetics would be recommended and a consultant geneticist copied into the final clinical report.

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.

Testing was not previously available in our lab for genes on this panel.

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

The two case studies below are real life cases from the renal tubulopathy clinic at GOSH:

1) A 1 year old girl is brought by her mother, who is known to be affected by autosomal dominant distal renal tubular acidosis (dRTA). The mother, as well as the grandmother each presented in their teens with renal stones. This is a typical presentation for this form of dRTA. A heterozygous mutation in *SLC4A1* has been identified in both using the panel test.

The child is below the 2nd percentile for height and weight, consistent with the height of mother and grandmother. Biochemical testing of the child shows no abnormality and renal ultrasound is normal. Based on this no treatment is commenced. Molecular testing of the child, however, confirms that she has inherited the mutation and alkali supplementation is commenced despite the normal plasma biochemistries.

At the next visit, the mother reports, that the child has more energy and appetite. This is objectively confirmed over follow-up by demonstration of catch-up growth. The child is now above the 9thpercentile for height and weight. (last follow-up age 5 years this). Ultrasound remains unremarkable. This child has avoided the painful typical complication of renal stones and the loss of growth potential, all of which was experienced by her mother and grandmother.

2) Pseudohypoaldosteronism type 1 (PHA1) is caused by an inability of the body to regulate sodium. Presenting in the first two weeks of life, infants fail to thrive and suffer dehydration; undiagnosed PHA1 is life-threatening. It can be caused by mutation in one of four genes.

In a boy thought to be affected, we identified a mutation in the *SCNN1G* gene by Next Generation Sequencing of a 12 gene panel and confirmed his diagnosis of PHA1.

When his baby sister was born genetic testing excluded the presence of the mutation in her first days of life. This provided reassurance & avoided the need for further blood tests and monitoring in the baby.

TESTING CRITERIA

33. Are previously approved Testing Criteria available that define the clinical entry point for this test? Yes/ Testing Criteria are available: http://ukgtn.nhs.uk/find-a-test/testing-criteria/

If No, please complete template. If yes please go to Q34 & 35.

For NGS panel tests, please complete a form for each clinical entry point/subpanel as described in Q2. Please contact the UKGTN office if you are unsure whether testing criteria is available.

34. If there is previously approved Testing Criteria that you agree to, please list below and provide the link to the Testing Criteria from the UKGTN website.

Testing criteria for:

1) Magnesium Related Renal Tubulopathies 10 Gene Panel (*FXYD2, TRPM6, EGF, HNF1B, CLDN16, CLDN19, KCNA1, KCNJ10, SLC12A3, CLCNKB*)

- HOMG1 (OMIM#602014), TRPM6
- HOMG2 (OMIM#154020), FXYD2
- HOMG3 (OMIM#248250), CLDN16
- HOMG4 (OMIM#611718), EGF
- HOMG5 (OMIM#248190), CLDN19
- Myokymia with hypomagnesaemia (OMIM£160120): KCNA1
- Gitelman syndrome (OMIM#263800):, SLC12A3
- EAST syndrome (OMIM#612780): KCNJ10
- Renal Cysts and Diabetes Syndrome (OMIM#137920): HNF1B
- Bartter syndrome type 3 (CLCNKB)

See below for testing criteria for 10 gene panel

2) Dent Disease 2 Gene Panel (*CLCN5, OCRL*)

- Dent disease type 1 (CLCN5)
- Dent disease type 2 (OCRL)

See below for testing criteria for 2 gene panel

3) Hypokalaemic Alkalosis (Bartter, Gitelman, EAST, Liddle) 8 Gene Panel (*SLC12A3, SLC12A1, KCNJ1, CLCKNB, BSND, KCNJ10, SCNN1B, SCNN1G*)

- Bartter syndrome, type 3 (http://ukgtn.nhs.uk/uploads/tx_ukgtn/Bartter_3_CLCNKB_TC_Oct_09.pdf)
- Gitelman syndrome (http://ukgtn.nhs.uk/uploads/tx_ukgtn/GSM_SLC12A3_TC_May11.pdf)
- EAST syndrome (http://ukgtn.nhs.uk/uploads/tx_ukgtn/East_Syndrome_KCNJ10_TC_Sept_11.pdf)
- Liddle syndrome *(* http://ukgtn.nhs.uk/find-a-test/search-by-disorder-gene/test-service/liddle-syndrome-258/)

See below for testing criteria for 8 gene panel

4) Hyperkalaemic Acidosis 8 Gene Panel *(WNK1, WNK4, KLHL3, CUL3, SCNN1A, SCNN1B, SCNN1G, NR3C2)*

- Pseudohypoaldosteronism type 1 (SCNN1A, SCNN1B, SCNN1G)
- (Pseudohypoaldosteronism type 2 or Gordon syndrome, (WNK1, WNK4, KLHL3, CUL3) see : http://ukgtn.nhs.uk/find-a-test/search-by-disorder-gene/test-service/pseudohypoaldosteronism-type-ii-4-gene-panel-750/)

5) Hypophosphatemia with Hypercalciuria 3 Gene Panel (SLC9A3R1, SLC34A1, SLC34A3)

See below for testing criteria for 3 gene panel

6) Autosomal dominant tubulointerstitial Kidney Disease 2 Gene Panel (UMOD, REN)

- Testing criteria available: (http://ukgtn.nhs.uk/uploads/tx_ukgtn/HNFJ12_MCKD2_UMOD_REN_TC_Sept_13.pdf)

See below for testing criteria for 2 gene panel

7) Nephrogenic Diabetes Insipidus 2 Gene Panel (*AQP2, AVPR2*)

- Nephrogenic diabetes insipidus (http://ukgtn.nhs.uk/uploads/tx_ukgtn/Diabetes_insipidus_AVPR2_TC_Sept_10.pdf)

8) Calcium Related Renal Tubulopathy 3 Gene Panel (*CASR, GNA11, AP2S1*)

- Hypocalciuric Hypercalcaemia (http://ukgtn.nhs.uk/uploads/tx_ukgtn/FHH_Type1_CASR_TC_Sept_12.pdf)

9) Renal Tubular Acidosis 4 Gene Panel (*SLC4A4, SLC4A1, ATP6V1B1, ATP6V0A4*)

- Recessive dRTA (http://ukgtn.nhs.uk/uploads/tx_ukgtn/RdRTA_ATP6V1B1_ATP6V0A4_TC_Sept_10.pdf)

UKGTN Testing Criteria

Test name: **Hypokalaemic Alkalosis and Hypomagnesia Disorders 10 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.**
Clinical Geneticist	
Consultant Paediatric Nephrologist	
Consultant Adult Nephrologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Biochemical indication of Magnesium Related Renal Tubulopathy **(**a plasma Mg value below the normal range (this changes with age) with evidence of renal magnesium wasting (Fractional exertion of >4%)) **AND** one or more of the following:	
• Nephrocalcinosis • Renal failure • Ocular/hearing defects • Polyuria • Polydipsia • Recurrent urinary tract infections • Recurrent renal colic • Seizures • Sensorineural deafness • Hypokalaemic alkalosis • Diabetes • Renal cysts • Myokymia	

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.

UKGTN Testing Criteria

Test name: **Dent Diseases 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.**
Clinical Geneticist	
Consultant Paediatric Nephrologist	
Consultant Adult Nephrologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
In male patients: Biochemical indication of Dent Disease i.e. Proteinuria and Hypercalcuria **AND one or more of the following:**	
• Nephrocalcinosis • Nephrolithiasis • Rachitic and Osteomalacic Bone Disease • Progressive kidney failure	

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.

UKGTN Testing Criteria

Test name: **Hypokalaemic Alkalosis 8 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.**
Clinical Geneticist	
Consultant Paediatric Nephrologist	
Consultant Adult Nephrologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Biochemical evidence of Hypokalaemic Alkalosis **AND** Decreased Renin **AND** Decreased Aldosterone **AND** one of the following:	
• Nephrocalcinosis • Hypercalciuria • Low blood pressure • Seizures • Sensorineural deafness	

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.

UKGTN Testing Criteria

Test name: **Pseudohypoaldosteronism, types I and II, 8 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.**
Clinical Geneticist	
Consultant Paediatric Nephrologist	
Consultant Adult Nephrologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Biochemical evidence of Hyperkalaemic Acidosis in urine **OR**	
Persistent Hyperkalaemic Acidosis despite high or normal aldosterone levels **OR**	
Infantile onset dehydration **AND** one of the following:	
• PHA1: Hypotension Skin rash Elevated sweat chloride Respiratory infections	
• PHA2: Hypertension	

Additional Information:
For infantile onset, there is the presence of no-anion gap metabolic acidosis with plasma potassium values above the normal range (this changes with age).

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.

UKGTN Testing Criteria

Test name: **Hypophosphatemia with Hypercalciuria Disorders 3 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.**
Clinical Geneticist	
Consultant Paediatric Nephrologist	
Consultant Adult Nephrologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Hypophosphatemia with Hypercalciuria (increased renal phosphate clearance) **AND**	
Rickets **OR** Short stature	

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.

UKGTN Testing Criteria

Test name: **Kidney Disease, Tubulo Interstitial, 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.**
Clinical Geneticist	
Consultant Paediatric Nephrologist	
Consultant Adult Nephrologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Hyperuricemia and decreased urinary excretion of urate **AND**	
Development of progressive chronic interstitial nephritis leading to renal impairment	

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.

UKGTN Testing Criteria

Test name: **Hyperparathyroidism and Related Calcium Renal Tubulopathies 3 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.**
Clinical Geneticist	
Consultant Paediatric Nephrologist	
Consultant Adult Nephrologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Individuals with confirmed idiopathic hypocalciuric hypercalcaemia	

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.

UKGTN Testing Criteria

Test name: **Diabetes Insipidus Disorders, Nephrogenic, 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.**
Clinical Geneticist	
Consultant Paediatric Nephrologist	
Consultant Adult Nephrologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Polyuria and Polydipsia with exclusion of Congenital Diabetes Insipidus **AND** Iatrogenic causes **AND**	
Measurement of urine AVP to identify renal resistance to its action	

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.

UKGTN Testing Criteria

Test name: **Renal Tubular Acidosis Disorders 4 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.**
Clinical Geneticist	
Consultant Paediatric Nephrologist	
Consultant Adult Nephrologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Spontaneous normal anion-gap metabolic acidosis	
OR oral acid-induced acidosis	
AND one or more of Hypercalciuria	
Hypokalemia	
Rickets	
Sensorineural Hearing Loss	

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 30

Family members where mutation is known 15

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.

1) admission for DDAVP test for patients at risk of NDI
2) admission for acid loading test for patients at risk of dRTA

	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)	Requiring Hospitalisation e.g. DDAVP / Acid loading	£2000
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)		**£2000**

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) **30**
Cost to provide tests for index cases if the genetic test in this Gene Dossier was not available (see Q39)	(b) £**2000**
Total annual costs pre genetic test submitted for evaluation in this Gene Dossier	(a) x (b) = (c) 30 x 2000 = £**60,000**
Total annual costs to provide genetic test	(a) x cost of genetic testing for index case = (d) 30 x 750 = £**22,500**
Additional savings for 100% positive rate for index cases	(d) – (c) = (e) 22,500 – 60,000 = £**-37,500**
Percentage of index cases estimated to be negative	(f) **15%**
Number of index cases estimated to be negative	(f) x number of index cases = (g) 0.15 x 30 = **4.5** rounded to **5**
Costs to provide additional tests for index cases testing negative	(g) x (b) = (h) 5 x 2000 = £**10,000**
Total savings for tests for index patient activity	(e) + (h) = (i) -37,500 + 10,000 = **£-27,500**
Total costs for family members	Costs for family member test x number of family members expected to test in a year (j) 185 x 15 = £**2775**
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) 185 x 10 = £**1850**
Total costs for family members minus any family member testing costs already provided	(j) – (k) = (l) 2775-1850 = £**925**
Additional savings for all activity expected in a year	(i) + (l) -27,500 + 925 = **£-26575**

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	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	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