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.

Ciliopathies gene panel – see appendix 1 for conditions

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:

The ciliopathies are a heterogeneous group of conditions with considerable phenotypic overlap. Analysis may be based on the following classifications; however it may be necessary for testing to be undertaken for the entire panel in patients where the diagnosis is unclear.
Ciliopathies sub-panels:

- Primary Ciliary Dyskinesia and RGMC (reduced generation of multiple motile cilia syndrome)
- Bardet Biedl Syndrome (HSS)
- Visceral Heterotaxy
- Orofaciodigital Syndrome
- Alstrom Syndrome (HSS)
- Meckel Syndrome
- Skeletal Ciliopathies
- Polycystic Kidney Disease, Nephronophthisis and Related Disorders
- Joubert Syndrome and Senior Loken Syndrome

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.

Ciliopathies are devastating congenital conditions that have in the last 10 years emerged as a major disease grouping of great medical impact. These inherited diseases are caused by defects in cilia, hair-like projections on most cells with roles in key human developmental processes via their motility and signalling functions. They are often lethal, and multiple organ systems are affected.

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

Ciliopathies are united in being genetically heterogeneous conditions and the different subtypes share clinical features, predominantly cystic kidney disease, but also retinal, respiratory, skeletal, hepatic and neurological defects in addition to metabolic defects, laterality defects and polydactyly. Their clinical variability can make them hard to recognise reflecting the ubiquity of cilia. Gene panels offer the only real solution to tackling the extensive number of candidate genes that need to be screened for each subtype. Ciliopathies are genetically heterogeneous affecting >1:2,000 births.

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.

Ciliopathies are in the majority autosomal recessive disease, with the exception of a few dominant and X-linked subtypes. See 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 appendix 1
6a. OMIM number(s) for gene(s) If a panel test – see 5. above
See appendix 1
6b. HGNC number(s) for gene(s) If a panel test – see 5. above
See 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.
Total genes: **122** (GenU band H if full panel tested) N.B. sum of sub-panels is greater than total number of genes since some genes are present in multiple sub-panels. **Genes by sub-panel:** Primary Ciliary Dyskinesia and Reduced Generation of Multiple Motile Cilia Syndrome (RGMC): **31** (GenU band G) Bardet Biedl Syndrome: **20** (GenU band G) Visceral Heterotaxy: **9** (GenU band G) Orofaciodigital Syndrome: **6** (GenU band G) Alstrom Syndrome: **1** (GenU band G) Meckel Syndrome: **9** (GenU band G) Skeletal Ciliopathies: **23** (GenU band G) (includes Ellis van Creveld, Sensenbrenner, SRTD & Jeune) Polycystic Kidney Disease, Nephronophthisis and Related Disorders: **22** (GenU band G) Joubert syndrome and Senior Loken Syndrome: **24** (GenU band G)
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.
Please see section 7a.
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.
This test uses SureSelect (Agilent) for enrichment of target regions followed by Illumina sequencing.
9b. For panel tests, please specify the strategy for dealing with gaps in coverage.
Gaps (i.e. bases in coding regions and flanking -14 to +6 intronic regions with less than 30 mapped reads) will not be routinely filled but coverage will be detailed in reports. Gaps may be filled on a case-by-case basis in response to results obtained, e.g. if a single heterozygous mutation is identified for a recessive condition where the gene shows incomplete coverage.
9c. Does the test include MLPA? **(For panel tests, please provide this information in appendix 1)**
See appendix 1

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.

The assay is provided in our laboratory.

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.

This test utilises an off-the-shelf clinical exome (Agilent SureSelect Focussed Exome) with added custom content to target additional required regions of the genome. Bioinformatic analysis will restrict variant calling to genes relevant to the clinical presentation, 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 Agilent SureSelect enrichment with Illumina sequencing, analysed with the in-house data analysis pipeline, has been validated using SNVs and small indels (1-6bp) detected by Sanger sequencing or by alternative NGS technology (n=155). In addition, nine positive control samples were run for validation and verification for this panel. All mutations, apart from a 22 base-pair duplication, were detected using the standard analysis pipeline. These figures have been included in the validation data below. Manual inspection showed that the 22 base-pair duplication was present in sequencing reads (28 out of 239 reads) but was below the threshold (20%) used for variant calling.
Three positive control CNVs were correctly called using ExomeDepth (http://cran.r-project.org/web/packages/ExomeDepth/index.html). Samples will routinely be checked for CNVs using this method and positives confirmed by qPCR or MLPA if available, however, the number of positive controls is insufficient to conclude that this method will robustly detect all CNVs. Mutation negative reports will therefore not state that CNVs have been excluded.
Due to the large number of genes included, it is not possible to give an accurate figure across the whole or sub-panels as to the predicted distribution of mutation type.

For panel tests:
Sensitivity 96.75-99.9% (95% CI)
Read depth minimum cut off: 30

	Previously tested	**NGS test concordant results**	**NGS False negative**
Number of patient samples			
Unique variants (total)	**169**		

SNV	**156**	**156**	**0**
Indel (1bp to 22bp)	**10**	**9**	**1**
CNV	**3**	**3**	**0**

If a reference sample (e.g. HapMap/CEPH DNA) has been tested please complete this table too: N/A

	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. 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?

We have been providing a full diagnostic service based on Sanger and NGS analysis for the BBS gene group since 2010.

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

Sanger Based Tests	NGS Based Tests
163	124

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

Sanger Based Tests	NGS Based Tests
156	112

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 diagnostic setting since April 2010.

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

Yes

13b. If yes, please provide details

Professor Phil Beales is the clinical lead for the national Bardet-Biedl syndrome service and has a research lab at the Institute of Child Health which studies ciliopathy related disorders.

Dr. Hannah Mitchison, Genetics and Genomic Medicine, UCL Institute of Child Health specialises in ciliopathies.

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.

EPIDEMIOLOGY

15a. Estimated prevalence of conditions in the general UK population
Prevalence is total number of persons with the condition(s) in a defined population at a specific time. 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
Please identify the information on which this is based.
For panel tests, please provide estimates for the conditions grouped by phenotypes being tested.

Primary Ciliary Dyskinesia and Reduced Generation of Multiple Motile Cilia Syndrome (RGMC): 1 per 15-20,000
Bardet Biedl Syndrome: 1 per 140-160,000
Visceral Heterotaxy: 1 per 10,000
Orofaciodigital Syndrome: 1 per 50-250,000
Alstrom Syndrome: 1 per <1:100, 000
Meckel Syndrome: 1 per 500,000
Skeletal Ciliopathies: 1 per 60,000 (figure from EVC used as highest contributor)
Polycystic Kidney Disease, Nephronophthisis and Related Disorders: 1 per 1000 (figure from PKD used as highest contributor)
Joubert Syndrome and Senior-Loken Syndrome: 1 per 80-100,000 (figure from Joubert Syndrome used as highest contributor)

15b. Estimated annual incidence of conditions in the general UK population
Incidence is total number of new 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.
For panel tests, please provide for groups of conditions.

Primary Ciliary Dyskinesia and Reduced Generation of Multiple Motile Cilia Syndrome (RGMC) : 36 new cases per year
Bardet Biedl Syndrome: 5 new cases per year
Visceral Heterotaxy: 72 new cases per year
Orofaciodigital Syndrome: 3-14 new cases per year
Alstrom Syndrome: 7 new cases per year
Meckel Syndrome: 1 new case per year
Skeletal Ciliopathies: 20 new cases per year
Polycystic Kidney Disease, Nephronophthisis and Related Disorders: 50 new cases per year
Joubert Syndrome and Senior-Loken Syndrome: 10 new cases per year
(figures based on general UK population)

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).

Since this test is not currently provided by our laboratory please see the details relating to the analytical sensitivity and specificity of the method as detailed in section 11**.**

21. Clinical sensitivity and specificity of test in target population

The *clinical sensitivity* of a test is the probability of a positive test result when condition is known to be present; the *clinical specificity* is the probability of a negative test result when disorder is known to be absent. The denominator in this case is the number with the disorder (for sensitivity) or the number without condition (for specificity).
Please provide the best estimate. UKGTN will request actual data after one year service.
For a panel test, the expected percentage diagnostic yield for the test in the target population can be presented as an alternative to clinical sensitivity and specificity?

Clinical sensitivity and specificity is expected to be high, although variants of uncertain pathogenicity may be identified during testing of affected or unaffected individuals.
Based on 317 BBS probands previously tested by this laboratory (not including sibling tests), 241 of whom had the diagnosis of BBS confirmed, the clinical sensitivity for this group is 76%. The clinical specificity is 100%.
On a validation run of 11 PCD patients, putative mutations were identified in nine, giving a sensitivity of 82%.
The clinical sensitivity for the remaining sub-panels will relate to the proportion of cases linked to loci which are not targeted by this test, due to the causative gene being as yet unidentified. Figures can be provided for all groups following provision of service.
The clinical specificity for all panels will be approaching 100%; the identification of variants of uncertain clinical significance would be likely in a patient with a misdiagnosis, but due to the high penetrance of the conditions tested the likelihood of identification of likely or clearly pathogenic mutations in keeping with inheritance patterns is small.

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.

Establishing a genetic diagnosis early in these patients allows their complex condition to be managed in a multidisciplinary setting and avoids the 'odyssey' associated with multiple clinics and diagnostic tests. In ciliopathies (e.g.Jeune syndrome) the type of genetic mutation can predict disease severity and organs likely to be affected in a way that clinical measures cannot.

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.

Different ciliopathy subtypes can be caused by mutations in the same gene, and this probably reflects the difficulties of making a precise clinical diagnosis in many ciliopathies. Gene testing is the only way to provide a conclusive test. Thus molecular testing has important implications for correct counselling of patients and ensures that their complex clinical needs can be met in a multidisciplinary environment.

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

The greatest is continued non-diagnosis of these devastating conditions. Clinical/genetic heterogeneity often results in a diagnostic odyssey impacting patient's lives and hindering disease management. Early interventions (e.g. in PKD, PCD) can improve disease outcomes, and mutation determination gives prognostic predictions (e.g in Jeune syndrome) for appropriate counselling and management. Without knowing the genetic diagnosis, PGD, prenatal screening and carrier testing could not be offered.

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.

For most ciliopathies, there are no clear diagnostic test outcomes and a clinical diagnosis is based on the presence in patients of enough combined phenotypic measures to predict the form of disease. A genetic test provides a gold standard confirmation, and is really an essential test for patients that is especially vital for less well characterised ciliopathies. There are exceptions: PKD clinical testing generally provides conclusive diagnosis, and for PCD a firm diagnosis can often be made based on identification of cilia structure defects combined with loss of motility. However, even in these two latter ciliopathies genetic testing is often able to provide conclusive diagnosis in patients that do not fit the classical disease picture, and our awareness of such patients is growing with the event of genetic testing – about 25% of PCD is inconclusive for the clinical tests available.

28. What unexpected findings could this test show? 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.

No unexpected findings outside the clinical phenotypes listed are expected.

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

LBR, SBDS: Biallelic mutations in SBDS lead to Shwachman Diamond syndrome; neonatal respiratory distress in these patients has been described to resemble Jeune syndrome. Danks *et al*. Arch. Dis. Child. 51: 697-701, 1976

Biallelic mutations in LBR lead to Greenberg Skeletal Dysplasia.

30. 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

31. 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.

We currently have a separate panel test for Bardet Biedl syndrome, the genes for which are now incorporated into this test.

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

None

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

Case study for Primary Ciliary Dyskinesia

An extended, consanguineous family with 6 children thought to be affected by PCD across three different family branches had proved to be difficult to diagnose in many of the affected individuals using the clinical measures. Cilia ultrastructure was normal in some affected children who also had had significant cilia motility preserved, whilst others showed absent dynein arms and static cilia, therefore a concrete diagnosis was hampered.

Genetic analysis showed two different PCD gene mutations segregating in this family; *DNAH11* responsible for normal cilia ultrastructure cases and *DNAI1* responsible for dynein arm loss cases. The *DNAH11* diagnosis in 4 siblings thought to be affected showed that one sibling did not carry the mutation. This was subsequently proven correct by re-visiting their clinical criteria, molecular confirmation providing additional benefit in these hard to diagnose cases.

Receiving a genetic diagnosis has several benefits, since clinical diagnosis is not always straightforward: around 20% of cases are considered difficult to diagnose definitively using clinical testing. Confirmation of diagnosis by molecular testing in the affected children has allowed their admittance to the national PCD management service, which involves a yearly clinic review, home and school visits, physiotherapy training, and correct genetic counselling on recurrence risk and carrier status for family members.

The genetic diagnosis furthermore allowed for appropriate guidance on grommet insertion surgery which can damage the ears and must be carefully considered. The clinic is also in a better position to advise on potential future infertility options: in PCD, infertility is common, with the exception to-date of *DNAH11* and *CCDC114* patients, who appear to have replacement proteins available in the sperm.

In this family's case, genetic diagnosis allowed one child to be discharged from clinic as unaffected with confidence, and the differential diagnosis outcome stopped all further testing on the other children to look for another diagnosis e.g. rare CF form, immunodeficiency.

Gaining a rapid DNA-based diagnosis of acilia is a further great help to family members / new siblings, since otherwise they often will undergo numerous invasive ciliary tests (nasal brush biopsy, bronchoscopy biopsy) to look for the cilia, before their acilia is fully appreciated and can help lead to reduction in the need for other diagnostic tests with their associated costs and delays. Prenatal diagnosis may also be considered in the family with a confirmed genetic diagnosis.

UKGTN Testing Criteria

Test name: Primary Ciliary Dyskinesia & Reduced Generation of Multiple Motile Cilia Syndrome (RGMC) 31 Gene Panel	
Approved name and symbol of disorder/condition(s): See Appendix 1	**OMIM number(s):**
Approved name and symbol of gene(s): See Appendix 1	**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 Paediatrician	
Consultant in Respiratory Medicine	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Neonate – at least one of the following: a) Situs inversus plus lower airway or nasal symptoms b) Persistent respiratory distress where other causes have been excluded c) Persistent rhinorrhoea and cough distress where other causes have been excluded d) Sibling with PCD	
Childhood – at least one of the following: a) Persistent lifelong wet cough (cystic fibrosis excluded) b) Unexplained bronchiectasis (cystic fibrosis excluded) c) Serious otitis media in association with recurrent lower and upper airway symptoms	
Adults - symptoms as above since early childhood, often associated with infertility or subfertility	

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: Bardet-Biedl Syndrome 20 Gene Panel	
Approved name and symbol of disorder/condition(s): See Appendix 1	**OMIM number(s):**
Approved name and symbol of gene(s): See Appendix 1	**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 Ophthalmologist	
Consultant Nephrologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Four primary features or three primary features and two secondary features	
Primary features:	
- Rod-cone dystrophy	
- Renal abnormalities	
- Obesity	
- Polydactyly	
- Learning difficulties	
- Hypogonadism in males	
Secondary features:	
- Speech disorder/delay	
- Strabismus/cataracts/astigmatism	
- Brachydactyly/syndactyly	
- Developmental delay	
- Polyuria/polydipsia	
- Ataxia/poor coordination/imbalance	
- Mild spasticity (especially lower limbs)	
- Diabetes mellitus	
- Dental crowding/hypodontia/small roots/high arched palate	
- Left ventricularhypertrophy/congenital heart disease	
- Hepatic fibrosis	

continued/…

Additional Information:

All referrals are via specialist NCG multidisciplinary clinics held at 4 Centres.

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: Alstrom Syndrome	
Approved name and symbol of disorder/condition(s): Alstrom Syndrome 1; ALMS	**OMIM number(s):** 203800
Approved name and symbol of gene(s): Centrosome and Basal Body Associated Protein; ALMS1	**OMIM number(s):** 606844

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 nephrologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
At least two of the following:	
- Hepatobiliary disease	
- Retinal degeneration	
- Childhood Onset Obesity	
- Renal Disease	
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.

UKGTN Testing Criteria

Test name: Orofaciodigital Syndrome 6 Gene Panel	
Approved name and symbol of disorder/condition(s): See Appendix 1	**OMIM number(s):**
Approved name and symbol of gene(s): See Appendix 1	**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	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
At least two of the following:	
- Abnormality of the oral cavity e.g. cleft or lobulated tongue, abnormal teeth, cleft palate.	
- Facial features e.g. cleft lip, wide nose, widely spaced eyes	
- Abnormal digits (polydactyly, syndactyly, clinodactyly)	

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: Skeletal Ciliopathies 23 Gene Panel	
Approved name and symbol of disorder/condition(s): See Appendix 1	**OMIM number(s):**
Approved name and symbol of gene(s): See Appendix 1	**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 nephrologist	
Consultant in metabolic diseases	
Consultant in retinal diseases	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
At least two of the following:	
- Renal cysts	
- Laterality defect	
- Polydactyly	
- Retinal degeneration	
- Posterior fossa defects/encephalocoele	
- Narrow thorax	

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: Polycystic kidney Disease, Nephronophthisis and Related Disorders 22 Gene Panel	
Approved name and symbol of disorder/condition(s): See Appendix 1	**OMIM number(s):**
Approved name and symbol of gene(s): See Appendix 1	**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 Nephrologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Renal cysts and one of the following:	
- Hepatobiliary disease	
- Laterality defect	
- Retinopathy	

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: **Joubert Syndrome and Senior-Loken Syndrome 24 Gene Panel**	
Approved name and symbol of disorder/condition(s): See Appendix 1	**OMIM number(s):**
Approved name and symbol of gene(s): See Appendix 1	**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	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Molar tooth sign on MRI and at least one of the following:	
- Eye movement disorder	
- Abnormal breathing pattern	
- Hypotonia evolving into ataxia	
- Developmental delay	

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: **Visceral Heterotaxy 9 Gene Panel**	
Approved name and symbol of disorder/condition(s): See Appendix 1	**OMIM number(s):**
Approved name and symbol of gene(s): See Appendix 1	**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	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Classical heterotaxy **OR**	
Non-classical heterotaxy (an isolated heterotaxy-type malformation **OR**	
Combination of malformations which may occur in heterotaxy but which are not diagnostic of heterotaxy (e.g. oesophageal atresia with intestinal malrotation)	

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: **Meckel Syndrome 9 Gene Panel**	
Approved name and symbol of disorder/condition(s): See Appendix 1	**OMIM number(s):**
Approved name and symbol of gene(s): See Apppendix 1	**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	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Meckel syndrome or related disorder, with at least two of the following:	
- Postaxial polydactyly	
- Cystic renal disease	
- Hepatic abnormalities, including portal fibrosis or ductal proliferation	
- Central nervous system malformation, including occipital, encephalocele, hydrocephaly or anencephaly	

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?

37. Based on experience what will be the national (UK wide) activity, per annum, for:

Index cases: 50

Family members where mutation is known: 50 (estimated 10 affected sibs, 40 parental samples)

38. 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

39. 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 if the index case has a definitive molecular genetic diagnosis from the test proposed in this gene dossier.

	Type of test	Cost (£)
Imaging procedures	Electron microscopy, High speed cilia motility video	400
Laboratory pathology tests (other than molecular/cyto genetic test proposed in this Gene Dossier)	Immunostaining, metabolic assays	Repeated & varied testing that is patient specific £500
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)		**£900**

40. Based on the expected annual activity of index cases (Q37), please calculate the estimated annual savings/investments based on information provided in Q39.

Number of index cases expected annually	(a) **50**
Cost to provide tests for index cases if the genetic test in this Gene Dossier was not available (see Q39)	(b) **900**
Total annual costs pre genetic test submitted for evaluation in this Gene Dossier	(a) x (b) = (c) **£45,000**
Total annual costs to provide genetic test	(a) x cost of genetic testing for index case = (d) 50 x £850 = **£42,500**
Additional savings for 100% positive rate for index cases	(d) – (c) = (e) 42500-45000 = **£-2500**
Percentage of index cases estimated to be negative	(f) **21%** based on PCD and BBS data
Number of index cases estimated to be negative	(f) x number of index cases = (g) 0.21 x 50 = **10.5**
Costs to provide additional tests for index cases testing negative	(g) x (b) = (h) 11 x 900 = **£9900**
Total investment for tests for index patient activity	(e) + (h) = (i) £-2500 + £9900 **= £7400**
Total costs for family members	Costs for family member test x number of family members expected to test in a year (j) 185 x 50 = **£9250** Based on two amplicons tested

If there is a genetic test already available and some of the family testing is already being provided, please advise the cost of the family testing already available	Cost for family member testing already available x estimated number of tests for family members already provided (k) **N/A** (Not yet available- Sanger sequence primers will be designed as appropriate when family members referred for testing)
Total costs for family members minus any family member testing costs already provided	(j) – (k) = (l) **£9250**
Additional marginal costs for all activity expected in a year	(i) + (l) £6950 + £9250 = **£16200**

41. 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. Genetic testing alerts significant clinical co-morbidities	Yes
2. Reduced mortality/saves lives	Yes
3. Avoids diagnostic invasive procedures/tests and associated in patient episodes	Yes
4. Confirms targeted therapy	No
5. Earlier diagnosis avoiding multi hospital appointments /procedures	Yes
6. Avoids irreversible harm	No
7. Enables access to educational and social support	Yes
8. At risk family members that test negative for a familial mutation can be discharged from follow up	Yes
9. At risk family members that test positive have appropriate follow up	Yes

Appendix 1

Genes in panel test and associated conditions (please expand table if required).

Rows that highlighted in yellow show where the gene is currently being analysed in the context of a single separate UKGTN test

NOTE: Some subpanels have been merged to reflect overlapping phenotypes. New panels inserted at the end of the table

OMIM standard name of condition	Mode of inheritance	OMIM No	HGNC symbol	HGNC standard name	HGNC No	OMIM No	Evidence of association between gene(s) and condition	% of horizontal coverage of gene	MLPA	Comments
Alstrom Syndrome Sub Panel										
Alstrom syndrome	AR	203800	ALMS1	Alstrom syndrome 1	428	203800	OMIM 203800	97.40%		
Bardet Biedl Syndrome Sub Panel										
Bardet-Biedl syndrome 3	AR	600151	ARL6	ADP-ribosylation factor-like 6	13210	608845	OMIM 608845	100.00%		
Bardet-Biedl syndrome 18	AR	615995	BBIP1	BBSome interacting protein 1	28093	613605	OMIM 613605	100.00%		
Bardet-Biedl syndrome 1	AR	209900	BBS1	Bardet-Biedl syndrome 1	966	209901	OMIM 209901	100.00%		
Bardet-Biedl syndrome 10	AR	615987	BBS10	Bardet-Biedl syndrome 10	26291	610148	OMIM 610148	100.00%		
Bardet-Biedl syndrome 12	AR	615989	BBS12	Bardet-Biedl syndrome 12	26648	610683	OMIM 610683	100.00%		
Bardet-Biedl syndrome 2	AR	615981	BBS2	Bardet-Biedl syndrome 2	967	606151	OMIM 606151	100.00%		
Bardet-Biedl syndrome 4	AR	615982	BBS4	Bardet-Biedl syndrome 4	969	600374	OMIM 600374	100.00%		
Bardet-Biedl syndrome 5	AR	615983	BBS5	Bardet-Biedl syndrome 5	970	603650	OMIM 603650	100.00%		
Bardet-Biedl syndrome 7	AR	615984	BBS7	Bardet-Biedl syndrome 7	18758	607590	OMIM 607590	100.00%		
Bardet-Biedl syndrome 9	AR	615986	BBS9	Bardet-Biedl syndrome 9	30000	615986	OMIM 615986	99.62%		

{Bardet-Biedl syndrome 1, modifier of}	AR	209900	CCDC28B	coiled-coil domain containing 28B	28163	610162	OMIM 610162	100.00%		
Bardet-Biedl syndrome 14	AR	615991	CEP290	centrosomal protein 290kDa	29021	610142	OMIM 610142	99.95%		
Bardet-Biedl syndrome 19	AR	615996	IFT27	intraflagellar transport 27	18626	615870	OMIM 615870	100.00%		
Bardet-Biedl syndrome 17	AR	615994	LZTFL1	leucine zipper transcription factor-like 1	6741	606568	OMIM 606568	100.00%		
Bardet-Biedl syndrome 6	AR	605231	MKKS	McKusick-Kaufman syndrome	7108	604896	OMIM 604896	99.86%		
Bardet-Biedl syndrome 13	AR	615990	MKS1	Meckel syndrome, type 1	7121	609883	OMIM 609883	100.00%		
Bardet-Biedl syndrome 16	AR	615993	SDCCAG8	serologically defined colon cancer antigen 8	10671	613524	OMIM 613524	100.00%		
Bardet-Biedl syndrome 11	AR	615988	TRIM32	tripartite motif containing 32	16380	602290	OMIM 602290	100.00%		
Bardet-Biedl syndrome 8	AR	615985	TTC8	tetratricopeptide repeat domain 8	20087	608132	OMIM 608132	100.00%		
Bardet-Biedl syndrome 15	AR	615992	WDPCP	WD repeat containing planar cell polarity effector	28027	613580	OMIM 613580	99.60%		
Meckel Syndrome Sub Panel										
Meckel syndrome 9	AR	614209	B9D1	B9 protein domain 1	24123	614144	OMIM 614144	100.00%		
Meckel syndrome 10	AR	614175	B9D2	B9 protein domain 2	28636	611951	OMIM 611951	100.00%		
Hydrolethalus syndrome	AR	236680	HYLS1	hydrolethalus syndrome 1	26558	610693	OMIM 610693	100.00%		
Meckel syndrome 8	AR	613885	TCTN2	tectonic family member 2	25774	613846	OMIM 613846	99.48%		

Meckel syndrome 1	AR	249000	MKS1	Meckel syndrome, type 1	7121	609883	OMIM 609883	100.00%		
Meckel syndrome 2	AR	603194	TMEM216	transmembrane protein 216	25018	613277	OMIM 613277	100.00%		
Meckel syndrome 3	AR	607361	TMEM67	transmembrane protein 67	28396	609884	OMIM 609884	100.00%		
Meckel syndrome 4	AR	611134	CEP290	centrosomal protein 290kDa	29021	610142	OMIM 610142	99.95%		
Meckel syndrome 7	AR	604387	NPHP3	nephronophthisis 3 (adolescent)	7907	608002	OMIM 608002	100.00%		
Orofaciodigital Syndrome Sub Panel										
Orofaciodigital syndrome I	XL	311200	OFD1	oral-facial-digital syndrome 1	2567	300170	OMIM 300170	100.00%		
Orofaciodigital syndrome IV	AR	258860	TCTN3	tectonic family member 3	24519	613847	OMIM 613847	99.98%		
Orofaciodigital syndrome XIV	AR	615948	C2CD3	C2 calcium-dependent domain containing 3	24564	615944	OMIM 615944	100.00%		
Orofaciodigital syndrome V	AR	174300	DDX59	DEAD (Asp-Glu-Ala-Asp) box polypeptide 59	25360	615464	OMIM 615464	100.00%		
No OMIM entry	AR	None	SCLT1	sodium channel and clathrin linker 1	26406	611399	Ciliary Genes TBC1D32/C6orf170 and SCLT1 are Mutated in Patients with OFD Type IX; Adly et al, 2013; Published online 6 November 2013 in Wiley Online Library (www.wiley.com/humanmutation). DOI: 10.1002/humu.22477	100.00%		

No OMIM entry	AR	None	TBC1D32	TBC1 domain family, member 32	21485	615867	Ciliary Genes TBC1D32/C6orf170 and SCLT1 are Mutated in Patients with OFD Type IX; Adly et al, 2013; Published online 6 November 2013 in Wiley Online Library (www.wiley.com/humanmutation). DOI: 10.1002/humu.22477	100.00%		
Primary Ciliary Dyskinesia and RGMC (reduced generation of multiple motile cilia syndrome) Sub Panel										
Ciliary dyskinesia, primary, 23	AR	615451	ARMC4	armadillo repeat containing 4	25583	615408	OMIM 615408	76.02%		Horizontal coverage to be addressed in next iteration of capture
Ciliary dyskinesia, primary, 26	AR	615500	C21orf59	chromosome 21 open reading frame 59	1301	615494	OMIM 615494	100.00%		
Ciliary dyskinesia, primary, 17	AR	614679	CCDC103	coiled-coil domain containing 103	32700	614677	OMIM 614677	100.00%		
Ciliary dyskinesia, primary, 20	AR	615067	CCDC114	coiled-coil domain containing 114	26560	615038	OMIM 615038	100.00%		
Ciliary dyskinesia, primary, 30	AR	616037	CCDC151	coiled-coil domain containing 151	28303	615956	OMIM 615956	100.00%		
Ciliary dyskinesia, primary, 14	AR	613807	CCDC39	coiled-coil domain containing 39	25244	613798	OMIM 613798	100.00%		
Ciliary dyskinesia, primary, 15	AR	613808	CCDC40	coiled-coil domain containing 40	26090	613799	OMIM 613799	94.35%		
Ciliary dyskinesia, primary, 27	AR	615504	CCDC65	coiled-coil domain containing 65	29937	611088	OMIM 611088	100.00%		
Ciliary diskinesia, primary, 29	AR	615872	CCNO	cyclin O	18576	607752	OMIM 607752	100.00%		

Ciliary dyskinesia, primary, 13	AR	613193	DNAAF1	dynein, axonemal, assembly factor 1	30539	613190	OMIM 613190	100.00%		
Ciliary dyskinesia, primary, 10	AR	612518	DNAAF2	dynein, axonemal, assembly factor 2	20188	612517	OMIM 612517	100.00%		
Ciliary dyskinesia, primary, 2	AR	606763	DNAAF3	dynein, axonemal, assembly factor 3	30492	614566	OMIM 614566	100.00%		
Ciliary dyskinesia, primary, 18	AR	614874	DNAAF5	dynein, axonemal, assembly factor 5	26013	614864	OMIM 614864	100.00%		
Ciliary dyskinesia, primary, 7, with or without situs inversus	AR	611884	DNAH11	dynein, axonemal, heavy chain 11	2942	603339	OMIM 603339	99.93%		
Ciliary dyskinesia, primary, 3, with or without situs inversus	AR	608644	DNAH5	dynein, axonemal, heavy chain 5	2950	603335	OMIM 603335	99.74%		
Ciliary dyskinesia, primary, 1, with or without situs inversus	AR	244400	DNAI1	dynein, axonemal, intermediate chain 1	2954	604366	OMIM 604366	100.00%		
Ciliary dyskinesia, primary, 9, with or without situs inversus	AR	612444	DNAI2	dynein, axonemal, intermediate chain 2	18744	605483	OMIM 605483	100.00%		
Ciliary dyskinesia, primary, 16	AR	614017	DNAL1	dynein, axonemal, light chain 1	23247	610062	OMIM 610062	100.00%		
Ciliary dyskinesia, primary, 21	AR	615294	DRC1	dynein regulatory complex subunit 1	24245	615288	OMIM 615288	100.00%		
Ciliary dyskinesia, primary, 25	AR	615482	DYX1C1	dyslexia susceptibility 1 candidate 1	21493	608706	OMIM 608706	99.94%		
Ciliary dyskinesia, primary, 5	AR	608647	HYDIN	HYDIN, axonemal central pair apparatus protein	19368	610812	OMIM 610812	90.95%		
Ciliary dyskinesia, primary, 19	AR	614935	LRRC6	leucine rich repeat containing 6	16725	614930	OMIM 614930	99.88%		

No OMIM entry	AR	None	MCIDAS	multiciliate differentiation and DNA synthesis associated cell cycle protein	40050	614086	MCIDAS mutations result in a mucociliary clearance disorder with reduced generation of multiple motile cilia. Boon et al, NATURE COMMUNICATIONS | 5:4418 | DOI: 10.1038/ncomms5418	100.00%		
Ciliary dyskinesia, primary, 6	AR	610852	NME8	NME/NM23 family member 8	16473	607421	OMIM 607421	100.00%		
Ciliary dyskinesia, primary, 24	AR	615481	RSPH1	radial spoke head 1 homolog (Chlamydomonas)	12371	609314	OMIM 609314	100.00%		
Ciliary dyskinesia, primary, 11	AR	612649	RSPH4A	radial spoke head 4 homolog A (Chlamydomonas)	21558	612647	OMIM 612647	100.00%		
Ciliary dyskinesia, primary, 12	AR	612650	RSPH9	radial spoke head 9 homolog (Chlamydomonas)	21057	612648	OMIM 612648	100.00%		
Ciliary dyskinesia, primary, 28	AR	615505	SPAG1	sperm associated antigen 1	11212	603395	OMIM 603395	100.00%		
Ciliary dyskinesia, primary, 22	AR	615444	ZMYND10	zinc finger, MYND-type containing 10	19412	607070	OMIM 607070	100.00%		
Cone-rod dystrophy, X-linked, 1	XL	304020	RPGR	retinitis pigmentosa GTPase regulator	10295	312610	OMIM 312610	100.00%		
Simpson-Golabi-Behmel syndrome, type 2	XL	300209	OFD1	oral-facial-digital syndrome 1	2567	300170	OMIM 300170	100.00%		
Visceral Heterotaxy Sub Panel										
Heterotaxy, visceral, 4, autosomal	AD	613751	ACVR2B	activin A receptor, type IIB	174	602730	OMIM 602730	100.00%		
Heterotaxy, visceral, 6, autosomal recessive	AR	614779	CFAP53	cilia and flagella associated protein 53	26530	614759	OMIM 614759	100.00%		

Heterotaxy, visceral, 2, autosomal	AD	605376	CFC1	cripto, FRL-1, cryptic family 1	18292	605194	OMIM 605194	100.00%		
Atrioventricular septal defect, partial, with heterotaxy syndrome	AD	606217	CRELD1	cysteine-rich with EGF-like domains 1	14630	607170	OMIM 607170	100.00%		
Transposition of great arteries, dextro-looped 3	AD	613854	GDF1	growth differentiation factor 1	4214	602880	OMIM 602880	97.70%		
Heterotaxy, visceral, 5	AD	270100	NODAL	nodal growth differentiation factor	7865	601265	OMIM 601265	100.00%		
Heterotaxy, visceral, 1, X-linked	XL	306955	ZIC3	Zic family member 3	12874	300265	OMIM 300265	100.00%		
Bardet-Biedl syndrome 17	AR	615994	LZTFL1	leucine zipper transcription factor-like 1	6741	606568	OMIM 606568	100.00%		
Nephronophthisis 4	AR	606966	NPHP4	nephronophthisis 4	19104	607215	OMIM 607215	100.00%		
Skeletal Ciliopathy Sub Panel										
No OMIM entry	AR	None	CEP120	centrosomal protein 120kDa	26690	None	A founder CEP120 mutation in Jeune asphyxiating thoracic dystrophy expands the role of centriolar proteins in skeletal ciliopathies. Shaheen et al, Human Molecular Genetics, 2014, 1–10, doi: 10.1093/hmg/ddu555	98.43%		
GREENBERG DYSPLASIA; GRBGD	AR	215140	LBR	lamin B receptor	6518	600024	OMIM 600024	100.00%		
Shwachman-Bodian-Diamond syndrome	AR	260400	SBDS	Shwachman-Bodian-Diamond syndrome	19440	607444	OMIM 607444	17.13%		Horizontal coverage to be

										addressed in next iteration of capture
Short-rib thoracic dysplasia 3 with or without polydactyly	AR	613091	DYNC2H1	dynein, cytoplasmic 2, heavy chain 1	2962	603297	OMIM 603297	99.85%		
Short-rib thoracic dysplasia 9 with or without polydactyly	AR	266920	IFT140	intraflagellar transport 140	29077	614620	OMIM 614620	99.89%		
Short-rib thoracic dysplasia 10 with or without polydactyly	AR	615630	IFT172	intraflagellar transport 172	30391	607386	OMIM 607386	100.00%		
Short-rib thoracic dysplasia 2 with or without polydactyly	AR	611263	IFT80	intraflagellar transport 80	29262	611177	OMIM 611177	99.96%		
Short-rib thoracic dysplasia 6 with or without polydactyly	AR	263520	NEK1	NIMA-related kinase 1	7744	604588	OMIM 604588	100.00%		
Short-rib thoracic dysplasia 11 with or without polydactyly	AR	615633	WDR34	WD repeat domain 34	28296	613363	OMIM 613363	100.00%		
Short-rib thoracic dysplasia 7 with or without polydactyly	AR	614091	WDR35	WD repeat domain 35	29250	613602	OMIM 613602	100.00%		
Short-rib thoracic dysplasia 8 with or without polydactyly	AR	615503	WDR60	WD repeat domain 60	21862	615462	OMIM 615462	99.64%		
CRANIOECTODERMAL DYSPLASIA 1; CED1	AR	218330	IFT122	intraflagellar transport 122	13556	606045	OMIM 606045	82.28%		Horizontal coverage to be addressed in next iteration of capture
Ellis-van Creveld	AR	225500	EVC	Ellis van Creveld	3497	604831	OMIM 604831	95.28%		

syndrome				syndrome						
Ellis-van Creveld syndrome	AR	225500	EVC2	Ellis van Creveld syndrome 2	19747	607261	OMIM 607261	98.11%		
?Cranioectodermal dysplasia 4	AR	614378	WDR19	WD repeat domain 19	18340	608151	OMIM 608151	99.83%		
Short-rib thoracic dysplasia 4 with or without polydactyly	AR	613819	TTC21B	tetratricopeptide repeat domain 21B	25660	612014	OMIM 612014	100.00%		
Joubert syndrome 21	AR	615636	CSPP1	centrosome and spindle pole associated protein 1	26193	611654	OMIM 611654	100.00%		
Cranioectodermal dysplasia 3	AR	614099	IFT43	intraflagellar transport 43	29669	614068	OMIM 614068	100.00%		
Joubert syndrome 2	AR	608091	TMEM216	transmembrane protein 216	25018	613277	OMIM 613277	100.00%		
Joubert syndrome 18	AR	614815	TCTN3	tectonic family member 3	24519	613847	OMIM 613847	99.98%		
Joubert syndrome 10	XL	300804	OFD1	oral-facial-digital syndrome 1	2567	300170	OMIM 300170	100.00%		
Orofaciodigital syndrome V	AR	174300	DDX59	DEAD (Asp-Glu-Ala-Asp) box polypeptide 59	25360	615464	OMIM 615464	100.00%		
Joubert syndrome 17	AR	614615	C5orf42	chromosome 5 open reading frame 42	25801	614571	OMIM 614571	100.00%		
Polycystic Kidney Disease, Nephronophthisis and Related Disorders Sub Panel										
Polycystic kidney disease, adult type I	AD	173900	PKD1	polycystic kidney disease 1 (autosomal dominant)	9008	601313	OMIM 601313	20.78%		Horizontal coverage to be addressed in next iteration of capture
Polycystic kidney	AD	613095	PKD2	polycystic kidney	9009	173910	OMIM 173910	99.13%		

disease 2				disease 2 (autosomal dominant)						
Polycystic kidney and hepatic disease	AR	263200	PKHD1	polycystic kidney and hepatic disease 1 (autosomal recessive)	9016	606702	OMIM 606702	99.99%		
Medullary cystic kidney disease 1	AD	174000	MUC1	mucin 1, cell surface associated	7508	158340	OMIM 158340	100.00%		
Medullary cystic kidney disease 2	AD	603860	UMOD	uromodulin	12559	191845	OMIM 191845	100.00%		
Polycystic liver disease	AD	174050	PRKCSH	protein kinase C substrate 80K-H	9411	177060	OMIM 177060	100.00%		
Polycystic liver disease	AD	174050	SEC63	SEC63 homolog (S. cerevisiae)	21082	608648	OMIM 608648	99.28%		
Nephronophthisis 16	AR	615382	ANKS6	ankyrin repeat and sterile alpha motif domain containing 6	26724	615370	OMIM 615370	98.31%		
Nephronophthisis 15	AR	614845	CEP164	centrosomal protein 164kDa	29182	614848	OMIM 614848	99.84%		
Nephronophthisis 18	AR	615862	CEP83	centrosomal protein 83kDa	17966	615847	OMIM 615847	100.00%		
Nephronophthisis 7	AR	611498	GLIS2	GLIS family zinc finger 2	29450	608539	OMIM 608539	100.00%		
Cranioectodermal dysplasia 3	AR	614099	IFT43	intraflagellar transport 43	29669	614068	OMIM 614068	100.00%		
Nephronophthisis 2, infantile	AR	602088	INVS	inversin	17870	243305	OMIM 243305	100.00%		
?Nephronophthisis 9	AR	613824	NEK8	NIMA-related kinase 8	13387	609799	OMIM 609799	100.00%		
Nephronophthisis 1, juvenile	AR	256100	NPHP1	nephronophthisis 1 (juvenile)	7905	607100	OMIM 607100	100.00%		
Nephronophthisis 3	AR	604387	NPHP3	nephronophthisis 3 (adolescent)	7907	608002	OMIM 608002	100.00%		

Nephronophthisis 4	AR	606966	NPHP4	nephronophthisis 4	19104	607215	OMIM 607215	100.00%		
Nephronophthisis 11	AR	613550	TMEM67	transmembrane protein 67	28396	609884	OMIM 609884	100.00%		
Nephronophthisis 12	AR	613820	TTC21B	tetratricopeptide repeat domain 21B	25660	612014	OMIM 612014	100.00%		
Nephronophthisis 13	AR	614377	WDR19	WD repeat domain 19	18340	608151	OMIM 608151	99.83%		
Nephronophthisis 14	AR/AD	614844	ZNF423	zinc finger protein 423	16762	604557	OMIM 604557	100.00%		
Renal cysts and diabetes syndrome	AD	137920	HNF1B	hnf1 homeobox b	11630	189907	OMIM 189907	100.00%		
Joubert Syndrome and Senior-Loken Syndrome Sub Panel										
Senior-Loken syndrome 5	AR	609254	IQCB1	IQ motif containing B1	28949	609237	OMIM 609237	100.00%		
Senior-Loken syndrome 8	AR	616307	WDR19	WD repeat domain 19	18340	608151	OMIM 608151	99.83%		
Senior-Loken syndrome 4	AR	606996	NPHP4	nephronophthisis 4	19104	607215	OMIM 607215	100.00%		
Senior-Loken syndrome 7	AR	613615	SDCCAG8	serologically defined colon cancer antigen 8	10671	613524	OMIM 613524	100.00%		
Joubert syndrome-3	AR	608629	AHI1	Abelson helper integration site 1	21575	608894	OMIM 608894	100.00%		
Joubert syndrome 8	AR	612291	ARL13B	ADP-ribosylation factor-like 13B	25419	608922	OMIM 608922	100.00%		
Joubert syndrome 17	AR	614615	C5orf42	chromosome 5 open reading frame 42	25801	614571	OMIM 614571	100.00%		
Joubert syndrome 9	AR	612285	CC2D2A	coiled-coil and C2 domain containing 2A	29253	612013	OMIM 612013	97.96%		
Joubert syndrome 21	AR	615636	CSPP1	centrosome and spindle pole associated protein	26193	611654	OMIM 611654	100.00%		

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Joubert syndrome 1	AR	213300	INPP5E	inositol polyphosphate-5-phosphatase, 72 kDa	21474	613037	OMIM 613037	100.00%		
Joubert syndrome 12	AR	200990	KIF7	kinesin family member 7	30497	611254	OMIM 611254	99.56%		
Joubert syndrome 10	XL	300804	OFD1	oral-facial-digital syndrome 1	2567	300170	OMIM 300170	100.00%		
?Joubert syndrome 22	AR	615665	PDE6D	phosphodiesterase 6D, cGMP-specific, rod, delta	8788	602676	OMIM 602676	100.00%		
Joubert syndrome 7	AR	611560	RPGRIP1L	RPGRIP1-like	29168	610937	OMIM 610937	98.25%		
Joubert syndrome 13	AR	614173	TCTN1	tectonic family member 1	26113	609863	OMIM 609863	98.68%		
Joubert syndrome 18	AR	614815	TCTN3	tectonic family member 3	24519	613847	OMIM 613847	99.98%		
Joubert syndrome 16	AR	614465	TMEM138	transmembrane protein 138	26944	614459	OMIM 614459	100.00%		
Joubert syndrome 2	AR	608091	TMEM216	transmembrane protein 216	25018	613277	OMIM 613277	100.00%		
Joubert syndrome 20	AR	614970	TMEM231	transmembrane protein 231	37234	614949	OMIM 614949	62.67%		Horizontal coverage to be addressed in next iteration of capture
Joubert syndrome 14	AR	614424	TMEM237	transmembrane protein 237	14432	614423	OMIM 614423	99.53%		
Joubert syndrome 15	AR	614464	CEP41	centrosomal protein 41kDa	12370	610523	OMIM 610523	99.89%		
Pallister-Hall syndrome	AD	146510	GLI3	GLI family zinc finger 3	4319	165240	OMIM 165240	100.00%		
Cone-rod dystrophy	AR	615973	POC1B	POC1 centriolar	30836	614784	OMIM 614784	100.00%		

20				protein B						
Joubert syndrome 19	AD	614844	ZNF423	zinc finger protein 423	16762	604557	OMIM 604557	100.00%		