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

Submitting laboratory: London NE 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 test name & the number of unique conditions across the whole of the panel test.

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

Dermatology 262 gene exome 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 – providing name of each sub panel.

Inherited conditions affecting the skin are a diverse group of genetically heterogeneous disorders. Analysis will typically be based on one of the sub-panels:

- Mendelian disorders of cornification / palmoplantar keratodermas
- Ectodermal disorders
- Connective/adipose tissue disorders
- RASopathies and pigmentary disorders
- Cutaneous vascular disorders
- Inflammatory skin disorders
- Progeroid/premature ageing syndromes
- DNA repair disorders
- Epidermolysis bullosa/skin fragility

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

This test is for a wide variety of diseases as there are many different genetic disorders which can involve the skin whether as primary skin disease or as a component of a genetic syndrome involving other body systems. They share a common significant impact on skin function, either with thick scaly skin, or fragile blistering skin, or extensive birthmarks predisposing to cancers. These therefore usually impact on quality of life, and in many cases on lifespan.

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

This test aims to provide testing for a wide variety of inherited and sporadic skin conditions with genetic aetiology. In order to provide testing which is appropriately specific but also reflecting the genetically heterogeneous nature of these conditions, ten sub-panels are offered based on the clinical presentation as follows:

Mendelian disorders of cornification / palmoplantar keratodermas

This group is comprised of inherited disorders of cornification of the skin which present as ichthyosis (dry, thickened scaly or flaky skin) and palmoplantar keratoderma (thickening of the skin on the hands and soles of the feet). Individuals affected with congenital ichthyosis frequently present at birth with a collodion membrane which is subsequently shed; the severity of the subsequent clinical course depending on the underlying genetic cause.

Ectodermal disorders

The ectodermal disorders (ectodermal dysplasia and related conditions) affect the teeth (anodontia/hypodontia), hair (hypotrichosis), nails (micronchyia/anonchyia) and sweat glands (hypohidrotic and anhidrotic forms). The different ectodermal dysplasia subtypes exhibit variation in the organs affected and show autosomal dominant, recessive and X-linked inheritance.

Connective/adipose tissue disorders

The connective/adipose tissue disorders are comprised principally of the Ehlers-Danlos syndrome group, exhibiting hyperextensibility of the skin, articular hypermobility and tissue fragility; the cutis laxa group, which show reduced elasticity of the skin and other connective and adipose tissue disorders include Loeys-Dietz syndrome, pseudoxanthoma elasticum, Buschke-Ollendorf syndrome, lipodystrophy and congenital restrictive dermopathy.

RASopathies and Pigmentary disorders

The pigmentary and RASopathies sub-panel covers a broad group of disorders showing abnormal pigmentation of the skin (hypo- or hyperpigmentation) or features (both cutaneous and multi-system) related to disorders of the RAS/MAPK pathway. Many of the pathogenic variants within these groups arise sporadically.

Cutaneous vascular disorders

The cutaneous vascular skin disorders group includes conditions characterised by telangiectasias (dilation of small blood vessels near the surface of the skin), capillary and venous malformations, angio-oedema and erythromelalgia.

Inflammatory skin disorders

Phenotypes encompassing the inflammatory skin disorders include pustular psoriasis, pityriasis rubra pilaris, chilblain lupus, severe childhood eczema with evidence of immune dysregulation, acrodermatitis enteropathica, cutaneous amyloidosis, erythrokeratodermia variabilis and manifestations consistent with diagnoses of Aicardi-Goutieres syndrome or incontinentia pigmenti.

Progeroid/Premature Ageing Syndromes

The progeroid/premature ageing group display skin manifestations (including variably: skin atrophy, telangiectasia, hyper/hypopigmentation, dry skin, loose/elastic skin) as well as variable additional syndromic features lending an appearance of premature senility.

DNA repair disorders

The DNA repair disorders group show a large variation in phenotype but are united by involvement in various DNA repair pathways. These are the nucleotide excision repair disorder group (xeroderma pigmentosum, Cockayne syndrome, trichothiodystrophy), for which the primary cutaneous phenotype is extreme sensitivity to ultraviolet light; the Fanconi anaemia group (double strand break repair pathway), which include Café-au-lait spots and/or skin pigmentation anomalies amongst other hallmark syndromic features; dyskeratosis congenita (telomere maintenance), characterised by abnormal skin pigmentation, nail dystrophy and leukoplakia of the oral mucosa and the mismatch repair pathway group, which show predisposition to skin tumours and Café-au-lait macules reminiscent of neurofibromatosis.

Epidermolysis bullosa/skin fragility

Epidermolysis bullosa (EB) is characterised by blistering of the skin and subsequent scarring and contractures of the joints. Additional members of this group are peeling skin syndrome and other syndromic disorders which include skin fragility or blistering.

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 Excel spread sheet appendix 1 and if there is only one mode of inheritance across all conditions, please state it here or if it varies please provide proportion split here.

Dermatological disorders may show autosomal dominant, autosomal recessive or X-linked inheritance and some conditions are predominantly *de novo* mosaic. 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 the Excel spread sheet, Appendix 1, available for download from the UKGTN website, and list all of the genes grouped by sub panels if applicable.

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:	262	GenU Band H
Sub-panels:		
Mendelian disorders of cornification / palmoplantar keratodermas	51	GenU Band H
Ectodermal disorders	63	GenU Band H
Connective/adipose tissue disorders	33	GenU Band G
RASopathies and pigmentary disorders	83	GenU Band H
Cutaneous vascular disorders	20	GenU Band G
Inflammatory skin disorders	25	GenU Band G
Progeroid/premature ageing Syndromes	10	GenU Band G
DNA repair disorders	38	GenU Band G
Epidermolysis bullosa/skin fragility	26	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 (based on 2016 version) that this test is assigned to for index case testing.
For NGS panel tests if there are sub panels, please provide GenU per subpanel.

See 7a

8. Mutational spectrum for which you test including details of known common mutations
(n/a for panel tests)

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 Consensus Coding Sequence (CCDS) exons and flanking +/-20bp intronic regions with less than 30 unambiguously 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. If the performance of the sub panels is expected to vary significantly to the data provided, please provide further details.

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/NextSeq/HiSeq sequencing instruments is conducted using an in-house developed pipeline of open-source tools, providing read alignment (BWA-MEM; Burrows Wheeler Aligner v0.7.5-a: http://bio-bwa.sourceforge.net/), variant calling (FreeBayes v0.9.21; https://github.com/ekg/freebayes) and variant annotation (Alamut-Batch v1.3.1; http://www.interactive-biosoftware.com/alamut-batch/). Pipeline output is limited to variants within 20 base pairs of the donor and acceptor splice sites of CCDS exons. Variants are filtered when present at 2% or greater in ExAC (overall frequency), exome variant server (EVS) or 1000 genomes datasets or in greater than three patients on a run.

The combination of Agilent SureSelect enrichment with Illumina sequencing, analysed with the in-house data analysis pipeline, has been validated using SNVs (n=152) and small indels (1-6bp)(n=3) detected by Sanger sequencing or by alternative NGS technology. In addition, nine positive control samples were run for validation and verification of the clinical exome (SNV n=4, Indel=7, CNV=3). 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 variant calling quality threshold.

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, 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.

Validation of the analysis pipeline has principally addressed the detection of germline variation. Whilst the variant calling algorithm has no lower read depth threshold for calling variants, the sensitivity to detect genuine variants at low alternate read percentages representing mosaicism has not been fully validated.

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 22 bp)	**10**	**9**	**1**
CNV	**3**	**3**	**0**

Further validation using the 'Genome-in-a-bottle' (GIAB) sample NA12878 has been included below. Variant validation was restricted to regions which were of high confidence in the GIAB NIST dataset (v. 3.3) and to regions covered by 30 or more reads in the clinical exome data. Since this dataset is significantly larger than the in-house dataset as described above, these data will be used for describing test sensitivity on clinical reports. Furthermore, since this process has highlighted the relatively poor sensitivity for the detection of indels, the single nucleotide variant and indel sensitivity figures will be quoted separately.

Average coverage across the target bases is 99.3%, therefore sensitivity figures have been adjusted to reflect this*.

A reference sample (eg HapMap/CEPH DNA) must have been tested, please complete this table:

	Known variants	NGS test concordant results	NGS False negative	Test sensitivity	*Adjusted test sensitivity	Test sensitivity (95% CI)
GIAB NA12878						
Unique variants (total)	5494	5449	45	99.18%	98.49%	98.22-98.7%
SNV	5240	5240	0	100%	99.3%	99.23-99.3%
Indel (1bp to 30 bp)	254	209	45	82.82%	82.24%	76.48-86.16%
CNV	0	N/A	N/A			

Specificity figures are not listed, since all clinically actionable reported variants are confirmed by Sanger sequencing. Therefore the combined specificity for these variants 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
0	15

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

Sanger Based Tests	NGS Based Tests
0	6

12d. Please provide the time period in which these reports have been produced and whether in a

research or a full clinical diagnostic setting.
From January 2016, in a full clinical diagnostic setting.
13a. Is there specialised local clinical/research expertise for this disorder?
Yes
13b. If yes, please provide details
Dr Veronica Kinsler is a consultant paediatric dermatologist and the academic lead clinician in the paediatric dermatology department, coordinating genetic research into rare dermatology disorders in children. As a Wellcome Trust Intermediate Fellow and Principal Investigator at the UCL Institute of Child Health she runs her team's research projects in these fields.
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

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.

Exact incidence or prevalence has been established for very few conditions covered here. The latest (Ninth) edition of the Rook's Textbook of Dermatology (considered the reference textbook) has been used as the reference base for this answer. The incidences of most conditions are estimated fall within the 1 in 20,000 to 1 in 100,000 range.

Since overall figures are not possible to obtain for each sub-panel, the following figures are given as surrogate prevalence/incidence for each panel, though these will be underestimates since they only represent a sub-set of each panel. Furthermore, some figures may represent particular rare forms of disease and more common causes may exist within the panels, despite figures being unknown:

Mendelian disorders of cornification / palmoplantar keratodermas:

Autosomal recessive congenital ichthyosis has an estimated prevalence of 1/200,000 (1)

Ectodermal disorders:

Hypohydrotic ectodermal dysplasia has an estimated incidence of 1/5-10,000 (2)

Connective/adipose tissue disorders:

Ehlers-Danlos syndrome type I has an estimated prevalence of 1/20,000 (3)

RASopathies and Pigmentary disorders:

Noonan syndrome has an estimated prevalence of 1/1000-2500 (4)

Oculocutaneous albinism type I has an estimated prevalence of 1/40,000 (5)

Cutaneous vascular disorders:

Ataxia telangiectasia has an estimated prevalence of 1/40-100,000 (6)

Inflammatory skin disorders:

Incontinentia pigmenti has an estimated incidence of 0.6-0.7/1,000,000 (7)

Progeroid/Premature Ageing Syndromes: very rare, no data available.

DNA repair disorders:

Xeroderma pigmentosum has an estimated prevalence of 1/1,000,000 (8)

Epidermolysis bullosa/skin fragility:

Epidermolysis Bullosa Simplex has an estimated prevalence of 1/30-50,000 (9)

(1) J Invest Dermatol. 2009 Jun;129(6):1421-8. doi: 10.1038/jid.2008.409
(2) Gene Reviews: Hypohydrotic Ectodermal Dysplasia (https://www.ncbi.nlm.nih.gov/books/NBK1112/)
(3) Gene Reviews: Ehlers-Danlos Syndrome, Classic Type (https://www.ncbi.nlm.nih.gov/books/NBK1244/)
(4) Gene Reviews: Noonan Syndrome (https://www.ncbi.nlm.nih.gov/books/NBK1124/)
(5) Gene Reviews: Oculocutaneous Albinism Type 1 (https://www.ncbi.nlm.nih.gov/books/NBK1166/)
(6) Gene Reviews: Ataxia-Telangiectasia (https://www.ncbi.nlm.nih.gov/books/NBK26468/)
(7) Gene Reviews: Incontinentia Pigmenti (https://www.ncbi.nlm.nih.gov/books/NBK1472/)
(8) Gene Reviews: Xeroderma pigmentosum (https://www.ncbi.nlm.nih.gov/books/NBK1397/)
(9) Gene Reviews: Epidermolysis Bullosa Simplex (https://www.ncbi.nlm.nih.gov/books/NBK1369/)

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).

The analytical sensitivity as shown in Q11 is 96.75-99.9% (95% CI) for single base substitutions and small insertion/deletions. The sensitivity to detect larger indels and CNVs is uncertain. The specificity of the test for reported likely pathogenic mutations will be approaching 100%, since these mutations are confirmed by Sanger sequencing.

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?

The diagnostic yield in cases tested to date is 40% (6/15), but a review of these figures, including sub-panels, will be made once larger numbers of referrals have been made to the service.

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.

The major impact on patients would be provision of an accurate genetic diagnosis for the first time. The availability of comprehensive genetic testing is a new service for most dermatology conditions. Patient management and alteration of clinical outcome will vary between diseases. Early genetic diagnosis in inherited disorders allows family planning, and prenatal diagnosis , as well as appropriate clinical management

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.

Currently there is very little comprehensive provision for dermatology genetic testing in the UK, and little or no provision for many conditions at a diagnostic level worldwide. For many of these disorders the same clinical phenotype is genetically highly heterogeneous.

Where conditions are shown to be inherited and with a significant recurrence risk, parental and wider family testing is available along with appropriate genetic counselling. Targeted pre-natal testing may then be offered as appropriate.

In addition, for inherited genetically heterogeneous conditions such as the Mendelian disorders of cornification, it is highly likely that improved recognition of distinct clinical phenotypes, and outcomes would be detected once genetically homogeneous groups were recognised. This in turn, will help define treatment options. This has already to be shown to be true for the ectodermal dysplasias, albeit with a smaller subset of genes than we are now offering.

For conditions that have an impact on organ systems in addition to the skin (e.g. RASopathies such as Neurofibromatosis type 1, Connective tissue disorders such as Loeys Dietz) then clinical diagnostic screening will be available as appropriate to manage the risk associated with the additional phenotypes (e.g. malignancy / aortopathy)

New medical therapies are hoped to replace the radical repeated episodes of surgery required for many of these diseases.

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

Prior to availability of this test, consequences include failure of accurate diagnosis, inability to offer pre-natal testing where possible, limited genetic counselling, failure to access novel medical therapies and continued dependence on limited traditional management options.

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

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.

Alternative means of diagnosis are only available for a small number of conditions and these do not allow for accurate sub-typing or for prenatal testing. These diseases would include the DNA repair disorders, and STS-deficient X-linked ichthyosis.

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.

A large number of the disorders on the dermatology panels include a skin phenotype in addition to other phenotypic features. In addition, genes in several sub-panels, particularly the DNA repair and RASopathy/pigmentary panels, are involved in cancer predisposition.

29. If testing highlights a condition that is very different from that being tested for, please outline your strategy for dealing with this situation.
If clearly pathogenic variants are identified in known cancer predisposition genes, where the finding is not thought to be directly related to the referral (e.g. heterozygous mutations in *BRCA2*, DNA repair panel), the mutation will be reported as an incidental finding with recommendation for referral to clinical genetics. The report would also be copied to clinical genetics and highlighted for discussion at the weekly cancer team meeting. A high proportion of the conditions in the DNA repair disorders panel are associated with increased cancer risk and therefore additional pre-test counselling is not warranted for the majority of referrals.
30. If a panel test, is this replacing an existing panel/multi gene test and/or other tests currently carried out by your lab e.g. Noonan Spectrum Disorders 12 Gene Panel replaced multigene Sanger test for KRAS, RAF1, PTPN11 and SOS1? If so, please provide details below.
N/A
31. Please describe any specific ethical, legal or social issues with this particular test.
None

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

Case 1: *PTPN11*

A seven year old boy was referred for testing on the pigmentary disorders sub-panel. He presented to the paediatric dermatology clinic with new onset multiple lentigines and learning difficulties. A possible RASopathy was suspected.

Analysis of the pigmentary disorders panel showed the patient to be heterozygous for variants in the *PTPN11*, *SAMD9*, *GNAS* and *PAX3* genes. The *GNAS* and *PAX3* variants are of uncertain clinical significance and although the *SAMD9* variant, a stop mutation, was considered likely to be pathogenic, no second mutation was identified in this gene and the phenotype associated with biallelic *SAMD9* mutations would not be consistent with the presentation.

The *PTPN11* variant, c.1493G>A; p.(Arg498Gln), affects a highly conserved amino acid at a position at which other missense mutations have been identified resulting in the clinical phenotype of Noonan syndrome with lentigines (formerly known as LEOPARD syndrome). This variant was therefore considered likely to be pathogenic and consistent with a diagnosis of Noonan with lentigines syndrome.

Due to the high incidence of hypertrophic cardiomyopathy in patients with Noonan syndrome with lentigines the patient was referred to cardiology for assessment. As a result of the relatively early confirmation of a molecular diagnosis this patient will receive timely cardiac monitoring any cardiac involvement can be managed before it becomes life threatening. The family may also access genetic counselling for information on recurrence risks and patient support groups.

Case 2: *TP63*

A 14 month old boy was referred for testing on the ectodermal dysplasia panel. He had cleft lip and palate, sparse hair and hypohydrosis.

Analysis of the ectodermal dysplasias panel identified a heterozygous variant in the *TP63* gene, c.1040G>T; p.(Cys347Phe). Despite being novel, this variant affects a highly conserved amino acid, *in silico* analysis is supportive of a deleterious effect and it is located in close proximity in the TP63 protein to other missense mutations causing *TP63*-related disease. This variant was therefore considered likely to be pathogenic, and parental follow up studies showed it be likely *de novo* in origin and provided support for this conclusion.

The family were counselled regarding the low recurrence risk and options for future pregnancies. *TP63* testing is available as a single gene test via UKGTN, but in this case due to the genetic heterogeneity of the condition sequential sequencing of genes associated with ectodermal dysplasia would likely have resulted in a longer and more costly route to diagnosis.

UKGTN Testing Criteria

Test name: Epidermolysis Bullosa/Skin Fragility 26 Gene Exome 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 Adult Dermatologist	
Consultant Paediatric Dermatologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Clinical signs of congenital and/or post-natal skin fragility or blistering **OR**	
Severe aplasia cutis congenita suggestive of epidermolysis bullosa **OR** Histopathological evidence of epidermolysis	

Additional Information:
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.

DNA REPAIR DISORDERS 38 GENE EXOME PANEL – TC BEING REVISED BY LAB TO ENSURE CONSISTENT WITH EXISTING TC – SM TO SIGN OFF

Additional Information:
For panel tests: If a specific pro forma is required to be completed, please attach it for review. The Testing Criteria for panel tests should be per clinical phenotype.
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.
A proforma is required to be completed for this testing, please access this from the laboratory website at (*please insert the link here*) *(delete if the test is not a panel test)*

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: Inflammatory Skin Disorders 25 Gene Exome 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 Adult Dermatologist	
Consultant Paediatric Dermatologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Recurrent episodes of pustular psoriasis **OR** Familial pityriasis rubra pilaris **OR** Recurrent episodes of chilblain lupus/clinical signs of Aicardi-Goutieres **OR** Severe childhood eczema with evidence of immune dysregulation **OR** Skin findings compatible with acrodermatitis enteropathica **AND** response to zinc supplementation **AND** relapse following zinc supplementation cessation when consuming normal amounts of zinc from diet **OR** Clinical findings compatible with cutaneous amyloidosis and amyloid deposition on skin biopsy **OR** Clinical findings compatible with erythrokeratodermia variabilis **OR** Clinical findings compatible with incontinentia pigmenti	

Additional Information:
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: Cutaneous Vascular Disorders 20 Gene Exome 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 Adult Dermatologist	
Consultant Paediatric Dermatologist	
Consultant Paediatric Immunologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Familial or multiple vascular malformations (vascular malformations as defined by the ISSVA classification) **OR** Familial or multiple telangiectasis **OR** Hereditary angio-oedema **OR** Clinical features consistent with erythromylagia/erythromelalgia	

Additional Information:
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: Progeroid/Premature Ageing Syndromes 10 Gene Exome 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 Adult Dermatologist	
Consultant Paediatric Dermatologist	

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 • Prematurely aged phenotype of post-natal onset • Progressive growth failure • Characteristic facies • Alopecia or hypotrichosis • Lipoatrophy or lipodystrophy • Joint stiffness or osteolysis • Early cardiovascular or cerebrovascular disease	

Additional Information:
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: RASopathies and Pigmentary Disorders 83 Gene Exome 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 Adult Dermatologist	
Consultant Paediatric Dermatologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Congenital abnormalities in skin pigmentation relative to unaffected skin areas or familial levels of pigmentation **OR**	
Congenital and persistent pigmentary lesions after 12 weeks of life **OR**	
Acquired persistent **OR** progressive pigmentary abnormalities where post-inflammatory changes have been considered and excluded **OR**	
Poikiloderma **OR**	
Suspected clinical diagnosis of Noonan syndrome or RAS/MAPK-related disorder including two of the following: - Short stature - Characteristic cardiac defects - Noonan facies	

Additional Information:
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: Connective/Adipose Tissue Disorders 33 Gene Exome 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 Adult Dermatologist	
Consultant Paediatric Dermatologist	
Consultant Adult Ophthalmologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Congenital cutis laxa **OR** Elastosis serpiginosa perforans **OR** Fulfillment of Villefranche criteria for Ehlers-Danlos Syndrome (please state which type) **OR** Skin changes typical of Pseudoxanthoma elasticum **OR** Retinal changes typical of Pseudoxanthoma elasticum **OR** Lipodystrophy or partial lipodystrophy (please state which) **OR** Congenital restrictive dermopathy leading to pulmonary compromise and/or joint contractures **OR** Multiple connective tissue naevi compatible with Buschke-Ollendorf syndrome **OR** Characteristic radiological features of Buschke-Ollendorf syndrome **OR** Characteristic clinical or histopathological skin findings of lipoid proteinosis	

Additional Information:
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: Ectodermal Disorders 63-Gene Exome 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 Adult Dermatologist	
Consultant Paediatric Dermatologist	
Consultant Paediatric Dental Surgeon	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Congenital/early-onset **AND** consistent abnormalities of at least one of • Hair – absent/abnormal • Teeth – absent/abnormal • Nails – absent/abnormal • Sweating – absent/decreased • Dermatoglyphics – absent **AND** where dermatophyte infection has been excluded (hair, nails, skin)	

Additional Information:
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: Palmoplantar Keratodermas and Cornification Mendelian Disorders 51-Gene Exome 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 Adult Dermatologist	
Consultant Paediatric Dermatologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Appropriate family history of ichthyosis or palmoplantar keratoderma **OR** Collodion baby **OR** Congenital ichthyosis **OR** Palmoplantar keratoderma	

Additional Information:
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: 100 (total for all conditions covered by the panel)

Family members where mutation is known: 50

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".

Our laboratory can provide the national need.

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

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

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

Many of the clinical diagnoses listed here are highly heterogeneous genetically, for example large groups of patients have a diagnosis of 'ichthyosis', but there are many genetic types, and these can have different non-cutaneous associated abnormalities (for example some ichthyoses are associated with neurological disease).

Similarly the different genetic types of ectodermal dysplasia, often very difficult to distinguish clinically particularly in the early years, can have very different clinical courses and implications for health (for example some ectodermal dysplasias are associated with a dangerous inability to sweat). The early genetic differentiation between different diseases will allow counselling of young families, prenatal testing where appropriate, and proper direction of patients to the correct patient care pathway.

In the example of Sjogren-Larsson ichthyosis early intervention with physiotherapy could conceivably improve outcomes, or in the example of hypohydrotic ectodermal dysplasia the careful lowering of children's temperature in hot weather could avoid the complication of febrile seizures (fever fits) which occur in overheating.

In addition, even in genetically more homogeneous disorders such as some of the RASopathies, these are nonetheless not always well differentiated clinically, and multiple repeat testing occurs to try to identify which gene is causative. The identification of the correct gene (as has been shown in one of our case studies) can lead to early channelling of patients to the right care, and avoidance of redundant and expensive follow up and testing in other areas.

	Type of test	Cost (£)

Imaging procedures		
Laboratory pathology tests (other than molecular/cyto genetic test proposed in this Gene Dossier)	Genetic testing; multiple single gene tests	£1000
Physiological tests (e.g. ECG)		
Other investigations/procedures (e.g. biopsy)	Skin biopsy & Histopathology	£500
Associated inpatient stays in the diagnostic pathway		
Total cost of tests/procedures to be stopped (please write n/a if the genetic test does not replace any other tests procedures in the diagnostic care pathway)	[redacted]	**£1250**
If any of the tests/procedures listed above would be carried out on individuals after having the genetic test because the genetic test did not pick up a pathogenic mutation (i.e. negatives), please indicate the costs for these tests to continue to diagnosis. ***For example a panel test replaces single gene tests that have been included above, but after the panel test an individual that tests negative would not need to have these single gene tests, because the genes were on the NGS panel.***		**£500 skin biopsy**

39. Please complete the Excel spread sheet available to download from the UKGTN website to calculate the estimated investment or savings, based on the expected annual activity of index & family cases (Q36 above) and using the information provided in Q38. Please submit this separately. ALL GENE DOSSIERS MUST INCLUDE THIS SPREAD SHEET

Excel spread sheet completed and submitted Yes

To note: If the new test is approved to be recommended for funding, the contents of the Excel finance sheet will be copied here. If the savings/investment differs per sub panel please complete a separate Excel spread sheet for each sub panel and rename the file to indicate the sub panel the Excel sheet refers to.

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. This information provides a useful guide to commissioners on the utility of the test.

For all sub-panels

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