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

Submitting laboratory: Cardiff RGC

1. Disorder/condition – approved name (please provide UK spelling if different from US) and symbol as published on the OMIM database (alternative names will be listed on the UKGTN website).
If NGS panel test, please provide a 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.

"Ectodermal Dysplasia Plus" 70 Gene Panel

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.

Panel test, please see appendix 1

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.

Ectodermal Dysplasia (ED) is a group of closely related conditions of which more than 150 different syndromes have been identified. The clinical effects can be highly variable both within a family and between different types of ED, but often include:

* life-threatening infection;
* a permanent susceptibility to overheating;
* a tendency to chest infection, chronic lung disease, eczema, asthma and atopy;
* malformations such as cleft palate, ectrodactyly (split hands and feet), absent Meibomian glands leading to dry sticky eye and ankyloblepharon (fusion of the eyelids) (in p63-related ED);
* hypodontia, oligodontia or anodontia and also the malformation of teeth;
* finally, but often the most difficult aspect of coping with ED, is the stigmatisation to which many affected individuals are subject, especially in adolescence.

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

Ectodermal Dysplasia (ED) is a group of closely related conditions of which more than 150 different syndromes have been identified. The Ectodermal Dysplasias (EDs) are genetic disorders affecting the development or function of the teeth, hair, nails and sweat glands. Other systems involved can include the lens or retina of the eye, parts of the inner ear, lungs and airways, the limbs, the nerves and other parts of the body. The various syndromes reported represent a different combination of these symptoms which can range from mild to severe. The clinical effects can be highly variable both within a family and between different types of ED, but often include:

* life-threatening infection and over-heating in early childhood (mortality in early childhood has been as high as 30% in some reports) and failure to thrive;
* a permanent susceptibility to overheating and heat stroke in adverse circumstances;
* a tendency to chest infection and chronic lung disease;
* a tendency to eczema, asthma and atopy;
* malformations such as cleft palate, ectrodactyly (split hands and feet), absent Meibomian glands leading to dry sticky eye and ankyloblepharon (fusion of the eyelids) (in p63-related ED);

* sparse scalp and body hair;
* hypodontia, oligodontia or anodontia and also the malformation of teeth (the paucity of teeth being usually treated with dentures, the protection of those teeth present and dental implants)
* finally, but often the most difficult aspect of coping with ED, is the stigmatisation to which many affected individuals are subject, especially in adolescence.

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.

Various modes of inheritance, please 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.

Panel test, please see appendix 1

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

If a panel test – see 5. above

Panel test, please see appendix 1

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

If a panel test – see 5. above

Panel test, please 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.

70

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.

H

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.

The Illumina TruSight One clinical exome and sub-panel approach shall be used for Ectodermal Dysplasia testing. First, DNA is randomly fragmented and tagged with universal adapter oligonucleotides through an enzymatic process known as 'tagmentation'. Thereafter the DNA library is amplified using primers containing indexes and motifs required for sample identification and Illumina sequencing. PCR products from twelve samples are pooled and target regions of interest captured through two sequential hybridisation reactions followed by a second amplification step. The enriched library is sequencing using Illumina Rapid Run reagents on an Illumina HiSeq 2500 sequencer.

Raw Illumina bcl files are first converted to FASTQ format with the Illumina Bcl2Fastq tool and processed using an in house bioinformatics pipeline developed using the Broad Institute best practise guidelines version 3. First, reads are aligned to the whole human reference genome build 37 (hg19) using BWA-

MEM and PCR amplification bias is mitigated by selecting reads with unique mapping locations for downstream analysis. Second, reads showing evidence of indels or aligned to known indel sites are re-aligned (GATK) before applying a base-quality score recalibration in order to improve the base-quality score accuracy (GATK). Finally variants are called using the GATK HaplotypeCaller and loosely hard-filtered to remove false-positive calls (< Q30) before annotation using the Ensembl Variant Effect Predictor. Annotated calls are imported into a custom NoSQL database, restricted to the appropriate sub-panel and filtered to remove calls greater than 5% in any population of 1000 genomes phase 3 or ExAC v0.3. Manual inspection of the remaining calls is performed using tools such as: SIFT, PolyPhen, MutationTaster, GERP++, PhyloP, PhastCons and classified according to ACGS recommendations.

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

Horizontal coverage and gaps will be reported to the requesting clinician with the option of filling using Sanger sequencing.

9c. Does the test include MLPA?

(For panel tests, please provide this information in appendix 1)

Yes, MLPA analysis for EDA, EDAR, EDARADD and WNT10A

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

Yes

10. Is the assay to be provided by the lab or is it to be outsourced to another provider?

If to be outsourced, please provide the name of the laboratory and a copy of their ISO certificate or their CPA number.

Provided by the All Wales Genetic 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.

Validation

Peripheral blood extracted DNA samples were collected from 32 patients with Ectodermal Dysplasia and 32 patient control samples. This cohort contained 69 unique variants identified using Sanger sequencing which were targeted for next-generation sequencing using the Illumina TruSight One clinical exome. The libraries were sequenced using five Illumina HiSeq 2500 rapid runs (Table 1.) Additionally, the CEPH cell-line control NA12878 was included on each run.

Run	NA12878	Clinical Samples
150716_D00501_0047_BHB092ADXX	1	10
150929_D00501_0050_AHYGMWADXX	1	11
151202_D00501_0062_AHG7YMBCXX	1	11
160513_D00501_0070_AHJYYYBCXX	1	16
160520_D00501_0071_BHK75FBCXX	1	16
Total	**5**	**64**

Table 1. Numbers of clinical samples run across five HiSeq 2500 rapid runs.

Bioinformatics approach

Raw Illumina bcl files were first converted to FASTQ format and processed using an in house bioinformatics pipeline developed using best practise guidance from the Broad Institute (see technical section). Raw variant calls were compared with genotypes already identified through routine diagnostic Sanger sequencing or the NIST Genome In a Bottle gold-standard (v2.18) for clinical and NA12878 samples respectively.

Sensitivity and reproducibility

Clinical samples

Assay sensitivity was 100.00% (94.79% to 100.00% 95CI).

	Previously tested	NGS test concordant results	NGS False negative
Number of patient samples	**64**		
Unique variants (total)	**69**	**69**	**0**
SNV	**53**	**53**	**0**
Indel (1bp to 36bp)	**16**	**16**	**0**
CNV	**0**	**0**	**0**

Table 1. Variants from clinical samples tested through this evaluation.

Specificity was not determined, all class 4-5 variants will be confirmed using an alternative method (i.e. Sanger sequencing).

Reference sample

NA12878 showed high concordance with the gold-standard and high inter-run reproducibility.

	Known variants	NGS test concordant results	NGS False negative
Reference sample details	**NA12878 (5 technical replicates)**		
Unique variants (total)	**5812**	**5794.2 ± 6.8**	**17.8 ± 6.8**
SNV	**5735**	**5717.6 ± 6.7**	**17.4 ± 6.7**
Indel (1bp to 43bp)	**77**	**76.6 ± 0.5**	**0.4 ± 0.5**
CNV	**0**	**0**	**0**

Table 2. Variants from reference control NA12878 tested through this evaluation.

Replicate	Sensitivity (95%CI)
1	99.71% (99.53% to 99.83%)
2	99.83% (99.68% to 99.92%)
3	99.54% (99.32% to 99.69%)
4	99.62% (99.43% to 99.76%)
5	99.78% (99.62% to 99.88%)

Table 2.1. Sensitivity of five NA12878 cell line replicates.

Determining minimum read depth (30x)

A single NA12878 dataset (with 5796 true-positive calls) was selected for random down-sampling using Picard across a range of 0.1%-1% in 0.1% increments and 1%-50% in 1% increments. The gold-standard variants identified in the full dataset were interrogated in each sub-sample. For each correct genotype the minimum read depth was recorded (Figure 1). A conservative minimum depth of 30x would correctly identify >99.8% (95% CI) calls.

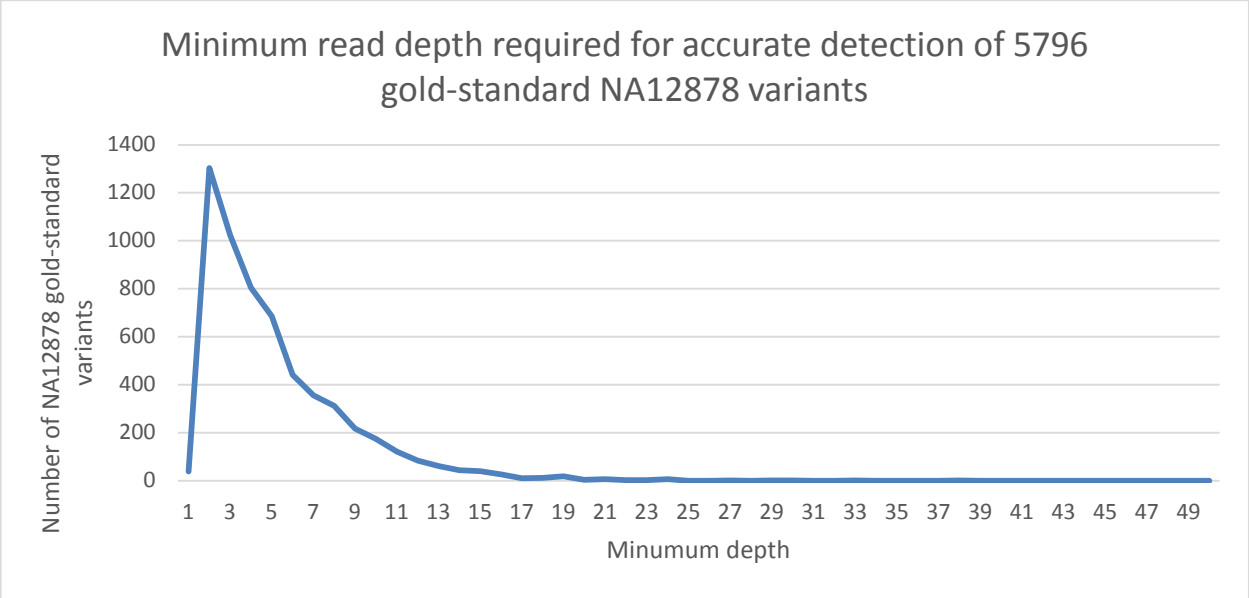

Figure 1. The minimum read depth required to indentify gold-standard variants in NA12878.

Horizontal coverage

The percentage of protein coding bases (+/-10bp; Ensembl build 82) covered to 30x or higher were recorded for each gene. The median value from a run of 32 patient samples was calculated (Table 4).

Gene	Median Coverage
ABCC9	94%
AIRE	94%
AXIN2	95%
BCS1L	100%
CDH3	88%
COG6	97%
COL11A1	99%
CTSC	96%
DKC1	98%
DLX3	95%
DLX5	96%
DOCK8	96%
DSC2	97%
DSP	98%
EDA	98%
EDA2R	100%
EDAR	95%

EDARADD	100%
ERCC2	100%
EVC	93%
EVC2	97%
FZD6	96%
GJA1	100%
GJB2	91%
GJB6	97%
GRHL2	99%
HR	98%
IFT122	97%
IFT43	100%
IKBKG	26%
IRF6	91%
JUP	99%
KRT1	100%
KRT14	100%
KRT16	100%
KRT17	100%
KRT6A	100%
KRT6B	67%
KRT74	93%
KRT85	96%
KRT9	99%
LIPH	96%
LPAR6	93%
LRP6	94%
LTBP3	95%
MBTPS2	96%
MSX1	83%
NFKBIA	99%
NLRP1	100%
NTRK1	100%
PAX9	98%
PIGL	79%
PKP1	97%
PORCN	100%
PTPRF	97%
PVRL1	97%
PVRL4	100%
RECQL4	97%
RHBDF2	98%
SATB2	92%
SHOC2	98%
SMARCAD1	97%
SMOC2	95%

TP63	91%
TRAF6	95%
TWIST2	96%
WDR19	99%
WDR35	97%
WNT10A	99%
WNT10B	93%

Table 4. Median percentage coverage of protein coding bases at greater than or equal to 30x across a single run of 32 patient samples.

12a. Are you providing this test already?

No, but we do offer Sanger sequencing testing and MLPA analysis for 7 of these genes

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

Sanger Based Tests	NGS Based Tests
>600	n/a

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

Sanger Based Tests	NGS Based Tests
371	n/a

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

Since approximately 2001 in a full clinical diagnostic setting for Sanger sequencing testing.

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

Yes

13b. If yes, please provide details

This laboratory has been providing testing for 7 of these genes individually for varying times and this testing is UKGTN approved. Professor Angus Clarke has extensive clinical and research experience in ectodermal dysplasia disorders. Professor Clarke's team in Cardiff has been involved in the international clinical trial for neonatal patients with XLHED. (Phase 2 Study to Evaluate Safety, Pharmacokinetics, Immunogenicity and Pharmacodynamics/Efficacy of EDI200 in Male Infants With X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED) (ECP-002)

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.

The precise incidence of ectodermal dysplasia is unknown, but could be as high as 22 per 100,000 (PMID:23416623)

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

Please identify the information on which this is based.

n/a for panel tests.

n/a

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

n/a for panel tests

n/a

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

n/a for panel tests.

n/a

INTENDED USE (Please use the questions in Annex A to inform your answers)

19. Please tick either yes or no for each clinical purpose listed.

Panel Tests: a panel test would not be used for pre symptomatic testing, carrier testing and pre natal testing as the familial mutation would already be known in this case and the full panel would not be required.

Diagnosis	☒ **Yes**	☐ **No**
Treatment	☐ **Yes**	☒ **No**
Prognosis & management	☒ **Yes**	☐ **No**
Presymptomatic testing (n/a for Panel Tests)	☐ **Yes**	☐ **No**
Carrier testing for family members (n/a for Panel Tests)	☐ **Yes**	☐ **No**
Prenatal testing (n/a for Panel Tests)	☐ **Yes**	☐ **No**

TEST CHARACTERISTICS

20. Analytical sensitivity and specificity

The *analytical sensitivity* of a test is the proportion of positive results correctly identified by the test (true positive/true positive + false negative). The *analytical specificity* of a test is the proportion of negative results correctly identified by the test (true negative/true negative + false positive).

This should be based on your own laboratory data for (a) the specific test being applied for or (b) the analytical sensitivity and specificity of the method/technique to be used in the case of a test yet to be set up. Please specify any types of mutations reported to cause the clinical phenotype that cannot be detected by the test.

Note that the preferred threshold is ≥95% sensitivity (with 95% Confidence Intervals).

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

Assay sensitivity was 100.00% (94.79% to 100.00% 95CI). The panel can detect single-nucleotide and small insertion-deletion (<~40bp) variants. This method has not been evaluated for copy-number detection although MLPA will be used for EDA, EDAR, EDARADD and WNT10A.

Specificity was not determined, all class 4-5 variants will be confirmed using an alternative method (i.e. 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?

Out of approximately 600 samples tested for EDA, EDAR, WNT10A and EDARADD, we have detected mutations in around 62% of patients.

We therefore, anticipate our clinical sensitivity will be at least ~50-70% and possibly higher, as we have more chance of establishing a diagnosis with this large panel of ED-related genes.

The specificity of the test will approach 100% as we are confident in usually being able to distinguish pathogenic from benign variants in these genes but we cannot be as certain about the clinicians' judgement.

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 test will help achieve accurate genetic diagnosis and establish inheritance patterns. This will aid in making informed decisions about management, prognosis and monitoring of patients for potential complications as well as other associated symptoms reported in the various syndromes. This will also help to provide advice for family members regarding reproductive risks. Targeted treatments are being developed for ectodermal dysplasia which will only be applicable to certain mutations/ genetic loci.

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.

These conditions show considerable phenotypic heterogeneity, providing the patient with a genetic diagnosis will clarify the recurrence risk (both for the patient's own children, their parents and the extended family) and open-up reproductive options (prenatal or pre-implantation genetic diagnosis). Using a single multi-gene panel will avoid the need for multiple visits to the Genetics Clinic to arrange sequential testing (generating a potential cost saving). Other unnecessary investigations may be avoided like skin biopsies, expensive sequential single gene testing. The family will be helped to anticipate problems and pre-empt them whenever possible. We know that mortality in early childhood is greater in first-born affected males in XHED families, and this is thought to be the result of the parents' acquisition of expertise in first recognising and then managing the condition. In addition, some specific problems (such as Xerophthalmia) may be recognised earlier and managed better if the diagnosis of ED is made at an early stage.

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.

It could potentially take longer for a confirmed diagnosis with continued uncertainty about nature of child's condition and laborious sequential testing of single genes. Some patients with ED would not receive a diagnosis. Family members would not have accurate recurrence risks affecting reproductive choices.

Patients would not be aware of any complications specific to this form of ED which could be minimised by early intervention.

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

n/a

27. Is there an alternative means of diagnosis or prediction that does not involve molecular diagnosis? If so (and in particular if there is a biochemical test), please state the added advantage of the molecular test.

No

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.

The gene panel includes some genes that are associated with syndromic disorders, learning difficulties, deafness, heart anomalies and increased risk of certain skin cancers.

AXIN2: oligodontia and colorectal cancer.

RHBDF2: oesophageal cancer

NTRK1: medullary thyroid carcinoma, familial

The possibility of an incidental finding of a potential health complication other than the obvious effects of an ectodermal dysplasia will always be mentioned.

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

The genes included in the panel are associated with a clinical phenotype of ectodermal problems; however, some genes can have additional phenotypes and this should be mentioned in the consent process prior to initiating the test. The Clinical Geneticist will review cases with the referring clinician to get additional information to help with interpretation and discuss potential impact of associated phenotypes.

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.

This test does include a selection of genes which are currently available as single gene tests, including EDA, EDAR, WNT10A, EDARADD, MSX2 and TP63. It is anticipated that where clinical suspicion strongly favours a particular gene Sanger sequencing would still be employed as a more economic option. However, if multiple genes are being considered, the panel will be activated.

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

None anticipated.

32. REAL LIFE CASE STUDY

Please provide a case study that illustrates the benefits of this test

A 14 year old boy was found to have typical features of hypohidrotic ectodermal dysplasia; his sister and mother both had several missing teeth. It was concluded that he would most likely have a mutation in the gene EDA and that these two relatives would most likely be heterozygous carrier females. It was not thought important to confirm the molecular basis of the pathology in this family until, some years later, our ED clinician was approached both through the family and by a clinical genetics colleague, in association with a pregnancy in the sister. The question was whether, if the child was an affected male (with a 25% probability), he could be recruited into a clinical trial of a new, protein-replacement treatment for the presumed diagnosis of X-linked HED associated with mutations in EDA. Timing was critical as the diagnosis would have to be established and the inpatient treatment started in the first 10-14 days of life. As a condition of potential recruitment to the trial, mutation testing was initiated in the pregnant woman and her brother, the known affected male. No mutation was found in EDA and so the search for mutations began to examine other loci, especially given the context of an ongoing pregnancy.

The outcome of the testing was that the affected male showed compound heterozygosity for mutations in EDAR while his sister was found to be a carrier of one of his two mutations. Mutations in EDAR often function as autosomal recessive alleles but some show a dominant effect in the heterozygous state. That was clearly happening in this family. As the mutations were in EDAR and not EDA, this couple would have a 1 in 2 chance of a heterozygous child, perhaps with minor features of ED but not with the severe effects found in males with sex-linked HED or in those, like the child's uncle, homozygous (or compound heterozygous) for EDAR mutations. The answer to the family's question, then, was that they were not at risk of a child with severe HED and would not be eligible for the clinical trial.

If a similar situation were to arise today, the lengthy process of clinical assessment and the debate among the family and with their professionals about what to do in the face of incomplete information, would now be entirely avoided, because of the rapidity of the molecular diagnosis. Because the mutation had not been determined in this family - in the index case, the pregnant woman's affected brother - much time, effort and energy were expended by the family and their professionals that could have been avoided.

UKGTN Testing Criteria

Test name: **"Ectodermal Dysplasia Plus" 70 gene panel**	
Approved name and symbol of disorder/condition(s): See separate Excel spreadsheet for list of disorders and genes	**OMIM number(s):**
Approved name and symbol of gene(s): See separate Excel spreadsheet for list of disorders and genes	**OMIM number(s):**

Referrals will only be accepted from one of the following:	
Referrer	**Tick if this refers to you.**
Consultant Clinical Geneticist	
Consultant Dermatologist, Adult	
Consultant Dermatologist, Paediatric	
Consultant Immunologist, Adult	
Consultant Immunologist, Paediatric	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Suspected diagnosis of ectodermal dysplasia and one or more of the following*:*	
Abnormalities of hair (hypotrichosis, sparse hair, sparse/missing eyebrows)	
Abnormalities of teeth (hypodontia, conical incisors)	
Abnormalities of skin (hypohidrosis, episodes of hyperthermia)	

Additional Information:

For panel tests:

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

If the sample does not fulfil the clinical criteria or you are not one of the specified types of referrer and you still feel that testing should be performed please contact the laboratory to discuss testing of the sample.

IS IT A REASONABLE COST TO THE PUBLIC?

36. Based on experience what will be the national (UK wide) expected activity for requesting this test, per annum, for:

Index cases 60

Family members where mutation is known 40

If a NGS panel test, it is recognised that the full panel will not be used to test family members where the familial mutation is known. Please provide expected number of tests to inform completion of Q40

37. If your laboratory does not have capacity to provide the full national need please suggest how the national requirement may be met.

For example, are you aware of any other labs (UKGTN members or otherwise) offering this test to NHS patients on a local area basis only? This question has been included in order to gauge if there could be any issues in equity of access for NHS patients. If you are unable to answer this question please write "unknown".

n/a

38. In order to establish the potential costs/savings that could be realised in the diagnostic care pathway, please list the tests/procedures that are no longer required to make a diagnosis for index cases where index cases 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.

	Type of test	Cost (£)
Imaging procedures		
Laboratory pathology tests (other than molecular/cyto genetic test proposed in this Gene Dossier)	"Repeat clinical appointments" Assuming an average of 4-5 genetic tests if done sequentially (Using case study example above) EDA EDAR WNT10A EDARADD GJB6 MSX1	£525 £250 £250 £160 £250 £160 £160
Physiological tests (e.g. ECG)	SWEAT TEST	£46
Other investigations/procedures (e.g. biopsy)	SKIN BIOPSY	£400.00
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)		**£2201**
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.***		**Possibly Skin biopsy = £400**

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

Number of index cases expected annually	60
Number of family member tests expected annually	40
Cost to provide a single test for an index case	£750
Cost to provide a single test for a family member	£160
Costs associated with tests/procedures for index cases if the genetic test in this Gene Dossier was not available	£2,201
Costs associated with tests/procedures for index cases that test negative for the genet Gene Dossier	£400
Total annual costs for diagnostic tests prior to introduction of the genetic test submitted for evaluation in this Gene Dossier	£132,060
Total annual costs to provide genetic test	£45,000
Additional savings or investment for 100% pick up rate for index cases	-£87,060
Percentage of index cases expected not to find a pathogenic mutation (negatives)	40%
Number of index cases estimated to not find a pathogenic mutation (negatives)	24
Costs or savings to provide additional tests for index cases that test negative	£9,600
Total savings / investment prior to application of marginal reduction if applicable	-£77,460
If a panel test and there are genes on the panel test that are already available on either other panel tests or single gene tests please estimate/suggest a marginal percentage reduction of the investment/savings. If you feel this is NOT applicable please leave this as 0%.	0%
Marginal percentage reduction if applicable applied to the savings/investment	£0
TOTAL SAVINGS for tests for INDEX CASES	**-£77,460**
Total costs for family members	£6,400
If family testing is already available for any of the genes on this panel across the Network, please estimate the associated funding for these tests.	£4,320
TOTAL INVESTMENT for tests for FAMILY MEMBERS	**£2,080**
ADDITIONAL SAVINGS FOR ALL ACTIVITY EXPECTED PER ANNUM	-£75,380

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.

Healthcare outcomes	Does this apply to this test?
1. Alerts significant clinical co-morbidities	Yes
2. Reduces mortality/saves lives	n/a
3. Avoids irreversible harm	n/a
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	No
6. Confirms targeted therapy/management	Not applicable currently
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