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

TEST – DISORDER/CONDITION – POPULATION TRIAD			
Submitting laboratory:	**London UCLH Biochemistry**	**Approved:**	**Sept 2013**
1. Disorder/condition – approved name and symbol as published on the OMIM database (alternative names will be listed on the UKGTN website)	3-BETA-HYDROXYSTEROID DEHYDROGENASE, TYPE II, DEFICIENCY OF		
2. OMIM number for disorder/condition	201810		
3a. Disorder/condition – please provide, in laymen's terms, a brief (2-5 sentences) description of how the disorder(s) affect individuals and prognosis.	This disorder affects synthesis of steroid hormones in the adrenals and gonads (testis and ovaries) with the result that there may be a degree of ambiguity in the development of the external genitalia in both males and females. In addition, lack of the adrenal steroids can cause loss of salt in the kidneys that can have fatal consequences if untreated.		
3b Disorder/condition – if required please expand on the description of the disorder provided in answer to Q3a.	The disorder is one of the rare causes of congenital adrenal hyperplasia, a disorder of sex development (DSD).		
4. Disorder/condition – mode of inheritance	Autosomal recessive		
5. Gene – approved name(s) and symbol as published on HGNC database (alternative names will be listed on the UKGTN website)	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 2; HSD3B2		
6a. OMIM number for gene(s) **6b HGNC number for gene(s)**	613890 5218		
7a. Gene – description(s)	4 exons		
7b. Number of amplicons to provide this test (molecular) or type of test (cytogenetic)	3		
7c. GenU band that this test is assigned to for index case testing	Band C		
8. Mutational spectrum for which you test including details of known common mutations	No common mutations. Analysis will involve sequence analysis of exons and intron-exon boundaries		
9a. Technical method(s)	PCR plus sequencing		
9b If a panel test using NGS please state if it is a conventional panel or a targeted exome test.			
9c. Panel/targeted exome Tests **i) Do the genes have 100% coverage? If not what is the strategy for dealing with the gaps in coverage?**			
ii) Does the test include MLPA?	No		
iii) Does this use sanger sequencing or Next Generation Sequencing (NGS)?	Sanger		
iv) If NGS is used, does the lab adhere to the Practice Guidelines for NGS?			
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.**	Provided by the lab		
11. Validation process	Sequenced one anonymous negative control. For		

Please explain how this test has been validated for use in your laboratory or submit your internal validation documentation	anonymous control material, surplus blood from HbA1c testing in the department was used. Our sequencing result was: normal gene sequence. Sequenced one known positive sample. The patient had previously been reported as homozygous for c.374T>G (p.Ile125Arg) in Germany by 'Humangenetik, Medizinisches Versorgungszentrum, Dr Eberhard & Partner, Dortmund'. The sample and a copy of their report were provided by the regional genetics laboratory service, Saint Mary's Hospital, Manchester. Our sequencing result was: c.374T>G (p.Ile125Arg) homozygous.
12a. Are you providing this test already?	☐ **Yes**
12b. If yes, how many reports have you produced? Please provide the time period in which these reports have been produced and whether in a research or a full clinical diagnostic setting.	3 Over the last year In clinical diagnostic setting
12c. Number of reports mutation positive	3
12d. Number of reports mutation negative	0
13. For how long have you been providing this service?	9 months
14a. Is there specialised local clinical/research expertise for this disorder?	☐ **Yes**
14b. If yes, please provide details	Lab is reference centre for biochemical diagnosis of urine steroid profiles. DSD clinic received tertiary referrals for diagnosis of this disorder.
15. Are you testing for other genes/disorders/conditions closely allied to this one? Please give details	Yes. Other causes of congenital adrenal hyperplasia: CYP11B1 and CY17 are analysed in this lab in addition to other steroid disorders which cause disorders of sex differentiation (SRD5A2 and HSD17B3).
16. Based on experience what will be the national (UK wide) activity, per annum, for:	
16a. Index cases	4
16b. Family members where mutation is known	12
17a. Does the laboratory have capacity to provide the expected national activity?	Yes
17b. If your laboratory does not have capacity to provide the full national need please could you provide information on 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. It is appreciated that some laboratories may not be able to answer this question. If this is the case please write "unknown".	
18. Please justify the requirement for another laboratory to provide this test e.g. insufficient national capacity.	

EPIDEMIOLOGY

19a. Estimated prevalence of condition in the general UK population	Figures unknown as is rare but probably <1/10[6].
19b. Estimated incidence of condition in the general UK population Please identify the information on which this is based	<1/10[6] There is no formal information on disease incidence.
20. Estimated gene frequency (Carrier frequency or allele frequency) Please identify the information on which this is based	0.12% Estimate based on number of cases diagnosed by our steroid profiling service compared to that of the more common, 21 hydroxylase deficiency which has a carrier frequency of 1/65.
21. Estimated penetrance Please identify the information on which this is based	Complete penetrance (based on literature reporting families with this disorder).
22. Estimated prevalence of condition in the population of people that meet the Testing Criteria.	5%

INTENDED USE

23. 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**
Treatment	☒ **No**
Prognosis & management	☐ **Yes**
Presymptomatic testing (n/a for panel tests)	☐ **No**
Carrier testing for family members (n/a for panel tests)	☐ **Yes**
Prenatal testing (n/a for panel tests)	☐ **Yes**

TEST CHARACTERISTICS

24. Analytical sensitivity and specificity This should be based on your own laboratory data for the specific test being applied for or the analytical sensitivity and specificity of the method/technique to be used in the case of a test yet to be set up.

Analytical sensitivity >99%

Analytical specificity >99%

25. 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).

Clinical sensitivity: >99%

All mutations to date have been identified within coding region or immediate intron-exon boundaries. There is however, always the possibility that mutations may arise deep in introns or promoter regions which are not examined by this analysis.

Clinical specificity: >95%

Some missense sequence variants have been described in the gene which could be misconstrued as of pathological significance in those not familiar with the field. As part of our service we keep an up to date list of variants, pathological and non-pathological.

26. 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).

Positive predictive value in target population approaching 100%

Negative predictive value in target population

99% (based on possibility of mutation occurring outside immediate coding regions)

27. Testing pathway for tests where more than one gene is to be tested 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.

CLINICAL UTILITY

28. How will the test change the management of the patient and/or alter clinical outcome?

For diagnosis and subsequent family testing.

The diagnosis of HSD3B2 deficiency can be made by biochemical means using a urine steroid profile looking for the characteristic delta 5 steroids. However, in the newborn period this can be problematic as the fetal adrenal cortex can also produce a similar profile. Once treated, the intermediates are suppressed and it can be quite problematic to stop treatment to retest. Genetic testing can get round this in suspected cases and can be used for family studies/prenatal dx.

Presentation

a) to paediatric endocrine team with ambiguous genitalia and/or salt losing crisis

b) clinical geneticist for prenatal studies/carrier studies.

29. Benefits of the test for the patient & other family members Please provide a summary of the overall benefits of this test.

1. A proper diagnosis is helpful to the patient

2. will allow a more informed debate regarding sex of rearing for those presenting early in life

3. will allow prenatal diagnosis.

30. What will be the consequences for patients and family members if this test is not approved?

There will be a lack of confirmatory testing for a disorder that has implications for both sexes of rearing and life-threatening salt-loss.

There will be no testing available for prenatal diagnosis.

31. 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.

Urine steroid profile, but as mentioned above, can get overlap with neonatal steroid profile.

Measurement of adrenal steroids in blood (notable DHA and androstenedione); however, as the current high throughput assays are less specific, this can lead to ambiguous results.

There is no alternative method for prenatal diagnosis.

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

None

33. Only complete this question if there is previously approved Testing Criteria and you do not agree with it.

Please provide revised Testing Criteria on the Testing Criteria form and explain here the changes and the reasons for the changes.

34. List the diagnostic tests/procedures that an index case no longer needs if this genetic test is available.

	Type of test	Cost (£)
Costs and type of imaging procedures	n/a	
Costs and types of laboratory pathology tests (other than molecular/cyto genetic test proposed in this gene dossier)	n/a	
Costs and types of physiological tests (e.g. ECG)	n/a	
Cost and types of other investigations/procedures (e.g. biopsy)	n/a	
Total cost tests/procedures no longer required		

35. Based on the expected annual activity of index cases (Q15a), please calculate the estimated annual savings/investments based on information provided in Q33.

Number of index cases expected annually	(a)
Cost to provide tests for index cases if the genetic test in this gene dossier was not available (see Q34)	(b)
Total annual costs pre genetic test	(a) x (b) = (c)
Total annual costs to provide genetic test	(a) x cost of genetic testing for index case = (d)
Total savings/investment	(c) – (d)

Such testing will not save any money but will provide a proper diagnosis and potentially prevent further disease in the family if prenatal diagnosis is used

36. REAL LIFE CASE STUDY
In collaboration with the clinical lead, describe TWO real case examples:

1. **prior to availability of genetic test**
2. **post availability of genetic test**

to illustrate how the test improves patient experience and the costs involved.

Case example one – pre genetic test

Patient presents at birth with ambiguous genitalia and on day 3 goes into a salt-losing crisis requiring treatment with mineralocorticoid and glucocorticoid. Differential diagnosis is a salt-losing form of congenital adrenal hyperplasia, CYP21, possibly CYP11B1 or HSD3B2. Parents advised not to register the birth of the patient until further testing done. Sample is taken for karyotype.

Urine steroid profile taken at day 3 showed increased delta 5 steroids but diagnosis ambiguous because of fetal adrenal steroid output. However, there are no characteristic metabolites of CYP21 or CYP11B1 present.

Further testing would require child to be taken off treatment with risk of salt loss or replacement with dexamethasone and use Synacthen test to promote excretion of abnormal metabolites.

PRE GENETIC TEST COSTS

	Type of test	Cost
Costs and type of imaging procedures		
Costs and type of laboratory pathology tests		
Costs and type of physiological tests (e.g. ECG)		
Cost and type of other investigations/procedures (e.g. biopsy)		
Cost outpatient consultations (genetics and non genetics)		
Total cost pre genetic test		**£**

Case example two – post genetic test

POST GENETIC TEST COSTS

	Type of test	Cost
Costs and type of imaging procedures		
Costs and types laboratory pathology tests (other than molecular/cyto genetic proposed in this gene dosier)		
Cost of genetic test proposing in this gene dossier		
Costs and type of physiological tests (e.g. ECG)		
Cost and type of other investigations/procedures (e.g. biopsy)		
Cost outpatient consultations (genetics and non genetics)		
Total cost post genetic test		**£**

As above scenario, but genetic testing would provide a definitive diagnosis without requirement to stop treatment. Imaging costs would be the same.

37. Estimated savings between two case examples described £
None.

UKGTN Testing Criteria

Test name: **3-Beta-Hydroxysteroid Dehydrogenase, Type II, Deficiency Of**	
Approved name and symbol of disorder/condition(s): 3-Beta-Hydroxysteroid Dehydrogenase, Type II, Deficiency of	**OMIM number(s):** 201810
Approved name and symbol of gene(s): hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 2; HSD3B2	**OMIM number(s):** 613890

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 Biochemist/Chemical Pathologist	
Consultant Paediatric or adult Endocrinologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Ambiguous genitalia **AND** at least one of the following: • Urine steroid profile suggestive of 3βHSD • Renal salt loss • abnormal ratio of DHA/androstenedione • failure of testosterone to increase on hCG test	
OR At risk family members where familial mutation is known.	

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.