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

Test – Disease – Population Triad

Disease – name	17-Beta Hydroxysteroid Dehydrogenase III Deficiency
OMIM number for disease	#264300
Disease – alternative names please provide any alternative names you wish listed	
Disease – please provide a brief description of the disease characteristics	17-Beta Hydroxysteroid Dehydrogenase III deficiency manifests in males as severe undermasculinization characterized by female external genitalia at birth. Such infants may have associated inguinal swellings from herniated testes, similar to what is seen in the complete androgen insensitivitysyndrome (CAIS). If the presentation is not at birth, sex assignment is female and virilisation occurs at puberty (hirsutism, increased musculature, deepening of the voice, clitoromegaly). This pubertal presentation is similar to 5-alpha-reductase deficiency. The internal genitalia are normal male. This disorder of sex development (DSD) is caused by inadequate testicular synthesis of testosterone due to a deficiency in the 17-beta hydroxysteroid dehydrogenase type III enzyme which converts androstenedione to testosterone. At the expected time of puberty, there is a marked increase in plasma LH and, consequently, in testicular secretion of androstenedione. Hence, a diagnostic hallmark of this disorder is a decreased plasma testosterone-to-androstenedione ratio(< 0.8) Significant amounts of the circulating androstenedione are, however, converted to testosterone, in peripheral tissues, by an unidentified member of the 17ß-HSD isozyme family, thereby causing virilization. Women who are homozygous or compound-heterozygous for mutations that, in men, cause 17ß-HSD 3 deficiency are asymptomatic.
Disease - mode of inheritance	Autosomal recessive
Gene – name(s)	17-Beta Hydroxysteroid Dehydrogenase III (HSD17B3)
OMIM number for gene(s)	605573
Gene – alternative names please provide any alternative names you wish listed	
Gene – description(s) (including number of amplicons).	The role of HSD17B3 is to convert androstenedione to testosterone in the testes. HSD17B3 contains 11 exons and is located on human chromosome 9q22.
Mutational spectrum for which you test including details of known common mutations.	Point mutations/small insertions/small deletions. Known common mutations include compound heterozygotes and missense mutations Arg80Gln and Cys268Tyr.
Technical Method (s)	Fluorescent Sequence analysis using mutation surveyor.

Approval Date: Sept 2010 Submitting laboratory: Cambridge Genetics Service

Validation Process Note: please explain how this test has been validated for use in your laboratory	Sequence analysis is used for mutation testing in a wide range of disorders in our laboratory. Known positive samples were tested initially for this disorder.
Are you providing this test already? **If yes, how many reports have you produced?** **Please give the number of mutation positive/negative samples you have reported**	Yes (on a research basis) **If Yes:** **Number of reports issued:** 36 **Number of reports mutation positive:** 20 **Number of reports mutation negative:** 16
For how long have you been providing this service?	5 years
Is there specialised local clinical/research expertise for this disease?	**Yes** | **~~No~~** | **Please provide details** Professor Hughes in the University of Cambridge Dept Paediatrics is a leader in the field of Disorders of Sex Development, including 17-Beta Hydroxysteroid Dehydrogenase III Deficiency.
Are you testing for other genes/diseases closely allied to this one? Please give details	Yes, we screen the Androgen receptor gene in cases of suspected Androgen Insensitivity Syndrome (AIS).
Your Current Activity If applicable - How many tests do you currently provide annually in your laboratory?	Index cases: 10 Family members where mutation is known: 5
Your Capacity if Gene Dossier approved How many tests will you be able to provide annually in your laboratory if this gene dossier is approved and recommended for NHS funding?	Index cases: 30 index cases plus relevant family members Family members where mutation is known: 50 cases
Based on experience how many tests will be required nationally (UK wide)? Please identify the information on which this is based	Index cases: 10 Family members where mutation is known: 20
National Activity **(England, Scotland, Wales & Northern Ireland)** **If your laboratory is unable 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".	We will be able to provide a UK-wide service

Epidemiology

Estimated prevalence of disease in the general UK population Please identify the information on which this is based	Estimated at 1:150,000 births based on prevalence in the Cambridge DSD database where 1.6% of all DSD cases are confirmed as having mutations in HSD17B3 mutations.
Estimated gene frequency (Carrier frequency or allele frequency) Please identify the information on which this is based	Approximately 25% of the 17-Beta Hydroxysteroid Dehydrogenase III Deficiency patients in the Cambridge DSD database were found to be compound heterozygotes for HSD17B3, suggesting that the carrier frequency is between 1:500 and 1:1000
Estimated penetrance Please identify the information on which this is based	In patients where the clinical presentation and Urinary Steroid Profile are indicative of 17-Beta Hydroxysteroid Dehydrogenase III Deficiency the incidence of HSD17B3 mutations is approximately 50% (Cambridge DSD database).
Target Population Description of the population to which this test will apply (i.e. description of the population as defined by the minimum criteria listed in the testing criteria)	Individuals with a clinical diagnosis of 17-Beta Hydroxysteroid Dehydrogenase III Deficiency, and their family members
Estimated prevalence of disease in the target population	50% in population with a clinical diagnosis of 17-Beta Hydroxysteroid Dehydrogenase III Deficiency.

Intended Use (Please use the questions in Annex A to inform your answers)

Please tick the relevant clinical purpose of testing	YES	NO
Diagnosis	√	
Treatment	√	
Prognosis & Management	√	
Presymptomatic testing		√
Risk Assessment for family members	√	
Risk Assessment – prenatal testing		√

Test Characteristics

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.	Sequencing coupled with Mutation Surveyor software has a sensitivity of >99% for point mutations/small insertions/small deletions
Clinical sensitivity and specificity of test in target population The *clinical sensitivity* of a test is the probability of a positive test result when disease is known to be present; the *clinical specificity* is the probability of a negative test result when disease is known to be absent. The denominator in this case is the number with the disease (for sensitivity) or the number without disease (for specificity)	Clinical sensitivity – we have detected HSD17B3 mutations in 50% of index cases. Clinical specificity >99%
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 disease or predisposition. It is measured by its *positive predictive value* (the probability of getting the disease given a positive test) and *negative predictive value* (the probability of not getting the disease given a negative test).	PPV >99% NPV >99%
Testing pathway 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 can be added to the document as a separate sheet if necessary.	N/A

Clinical utility of test in target population (Please refer to Appendix A) Please provide a description of the clinical care pathway.	The main differential for this cause of DSD is CAIS for a presentation in infancy, and 5-alpha-reductase deficiency when the presentation is at puberty with virilisation of a female. All female infants with bilateral inguinal swellings should be investigated for testes as being the possible cause of the swellings. The surgeon at the time of hernia repair may locate gonads in the hernial sac and biopsy them. A karyotype is also performed. If testes and a 46,XY karyotype are confirmed, the main differential is CAIS or 17HSD deficiency. Biochemical tests on serum and urine may not be confirmatory for either possibility, thus making genetic testing mandatory. Presentation at puberty is an easier diagnosis where the biochemical tests are more reliable (markedly elevated serum androstenedione and typical urinary steroid profile). The main differential is 5-alpha-reductase deficiency. Genetic tests are required to confirm the correct diagnosis. Andersson S, Moghrabi N. Physiology and molecular genetics of 17 beta-hydroxysteroid dehydrogenases. Steroids 1997;62:143-147. Moghrabi N, Hughes IA, Dunaif A et al. Deleterious missenses mutations and silent polymorphism in the human 17 beta-hydroxysteroid dehydrogenase 3 gene (HSD17B3). J Clin Endocrinol Metab 1998;83:2855-2860 Achermann JC, Hughes IA. Disorders of sex development. In, Williams Textbook of Endocrinology, 11th Edition, 2007.
How will the test add to the management of the patient or alter clinical outcome?	Important to distinguish from CAIS which is an X-linked disorder. Also, if the presentation is before puberty, it is important to perform gonadectomy before puberty in view of the occurrence of virilisation. This does not occur in CAIS.
What impact will this test have on the NHS i.e. by removing the need for alternative management and/or investigations for this clinical population? Please provide evidence from your own service.	Alternative investigations are not very reliable in this disorder, particularly the use of urinary steroid analysis. This test cannot be used in infancy but is more reliable at pubertal presentation. Serum androstenedione is typically elevated in 17HSD deficiency but this is not always the case in infancy.
What are the consequences of not doing this genetic test. Commissioners have asked for specific information to support introduction of tests.	Missed or wrong diagnosis, with the consequences referred to above. If the gonads are left in situ and sex assignment is female, marked virilisation will occur at puberty with all the consequent distress for the patient.
Utility of test in the NHS In a couple of sentences explain the utility of this test for the disease(s)	This gene test is the only reliable test available to make a definitive diagnosis of this enzyme deficiency
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. The steroid ratio calculation in serum is not always < 0.8 in proven cases and the urinary steroid analysis is only reliable after puberty.

Please describe any specific ethical, legal or social issues with this particular test?	No more than for any condition due to a single gene disorder

UKGTN Testing criteria

Name of Disease(s): 17-@BETA HYDROXYSTEROID DEHYDROGENASE III DEFICIENCY (264300)

Name of gene(s): Hydroxysteroid (17-beta) dehydrogenase 3; HSD17B3 (605573)

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	
Paediatric/Adult Endocrinologist	
Adolescent Gynaecologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:

Criteria	Tick if this patient meets criteria
Ratio of testosterone to androstenedione < 0.8 **AND**	
Inguinal swellings in apparent newborn female **AND**	
Some newborn clitoromegaly **OR**	
Virilisation of female at puberty	

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.

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