

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

TEST – DISEASE/CONDITION – POPULATION TRIAD	
Submitting laboratory:	Cambridge RGC
Approved:	September 2012
1. Disease/condition – approved name and symbol as published on the OMIM database (alternative names will be listed on the UKGTN website)	46, XY SEX REVERSAL 3; SRXY3
2. OMIM number for disease/condition	612965
3. Disease/condition – please provide a brief description of the characteristics of the disease/condition and prognosis for affected individuals. Please provide this information in laymen’s terms.	46,XY disorder of sex development (46,XY DSD) is characterized by a 46, XY karyotype and ambiguous genitalia with mild to severe penoscrotal hypospadias with or without chordee, dysgenetic testes, reduced to no sperm production, and müllerian structures that range from absent to presence of a fully developed uterus and fallopian tubes. 46, XY complete gonadal dysgenesis (46, XY CGD) is characterized by a 46, XY karyotype, normal female external genitalia, completely undeveloped (“streak”) gonads, no sperm production, and presence of normal müllerian structures.
4. Disease/condition – mode of inheritance	Autosomal recessive/dominant
5. Gene – approved name(s) and symbol as published on HUGO database (alternative names will be listed on the UKGTN website)	Nuclear receptor subfamily 5, group A, Member 1 NR5A1
6. OMIM number for gene(s)	184757
7. Gene – description(s)	NR5A1 is an orphan nuclear receptor which regulates multiple genes involved in adrenal and gonadal development. It has 6 functioning exons (2,3,4,5,6,7) split into 10 PCR reactions.
7b. Number of amplicons to provide this test	10 amplicons
7c. MoIU/Cyto band that this test is assigned to	These would all be in band D
8. Mutational spectrum for which you test including details of known common mutations	We will screen for nonsense and missense mutations, splice site mutations, small insertions and deletions in these genes. We will also offer testing for whole exon deletions and duplications.
9. Technical method(s)	Fluorescent sequence analysis using mutation surveyor. MLPA analysis using MRC Holland kit.
10. Validation process Please explain how this test has been validated for use in your laboratory	Sequence and dosage analysis is used for mutation testing in a wide range of disorders in our laboratory – therefore these methods are already validated within the lab.
11a. Are you providing this test already?	Yes

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11b. If yes, how many reports have you produced?	25 on a research basis
11c. Number of reports mutation positive	6
11d. Number of reports mutation negative	19
12. For how long have you been providing this service?	2 years
13a. Is there specialised local clinical/research expertise for this disease?	Yes
13b. If yes, please provide details	Professor Hughes in University of Cambridge Dept Paediatrics in conjunction with John Achermann, Institute of Child Health, London.
14. Are you testing for other genes/diseases/conditions closely allied to this one? Please give details	Yes. Androgen Receptor, SRD5A2, HSD17B3 and SRY in addition of NR5A1 will complete a package of candidate gene analysis relevant to a molecular diagnosis of XY DSD.
Your current activity If applicable - How many tests do you currently provide annually in your laboratory?	25
15a. Index cases	25
15b. Family members where mutation is known	10
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?	We will be able to meet the capacity for the UK
16a. Index cases	
16b. Family members where mutation is known	
Based on experience how many tests will be required nationally (UK wide) per annum? Please identify the information on which this is based	50 Based on Cambridge DSD database gonadal dysgenesis cases, this number is constantly changing as the parameters for the phenotype are wide.
17a. Index cases	50
17b. Family members where mutation is known	30
18. 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".	

EPIDEMIOLOGY	
19. Estimated prevalence of condition in the general UK population Please identify the information on which this is based	Unknown
20. Estimated gene frequency (Carrier frequency or allele frequency) Please identify the information on which this is based	Not known
21. Estimated penetrance Please identify the information on which this is based	N/A
22. Estimated prevalence of condition in the target population. The target population is the group of people that meet the minimum criteria as listed in the Testing Criteria.	Estimated prevalence is difficult to state based on the definition of the disease condition quoted in Item 3. Overall, the prevalence of NR5A1 mutations in patients with a clinical diagnosis of gonadal dysgenesis is 10-15% from published studies. The Cambridge series of mutations found in 6 patients with partial gonadal-dysgenesis (based on a robust clinical diagnosis) reports a higher prevalence of 24%.
INTENDED USE	
23. Please tick the relevant clinical purpose of testing	
Diagnosis	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Treatment	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Prognosis & management	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Presymptomatic testing	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Carrier testing for family members	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Prenatal testing	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

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.

>99% for uni-directional sequencing analysed with Mutation Surveyor

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 disease is known to be absent. The denominator in this case is the number with the disease (for sensitivity) or the number without condition (for specificity).

Not possible to provide figures because of difficulties currently in defining the denominator in view of the widely defined clinical phenotype (see 22).

26. Clinical validity (positive and negative predictive value in the target population)

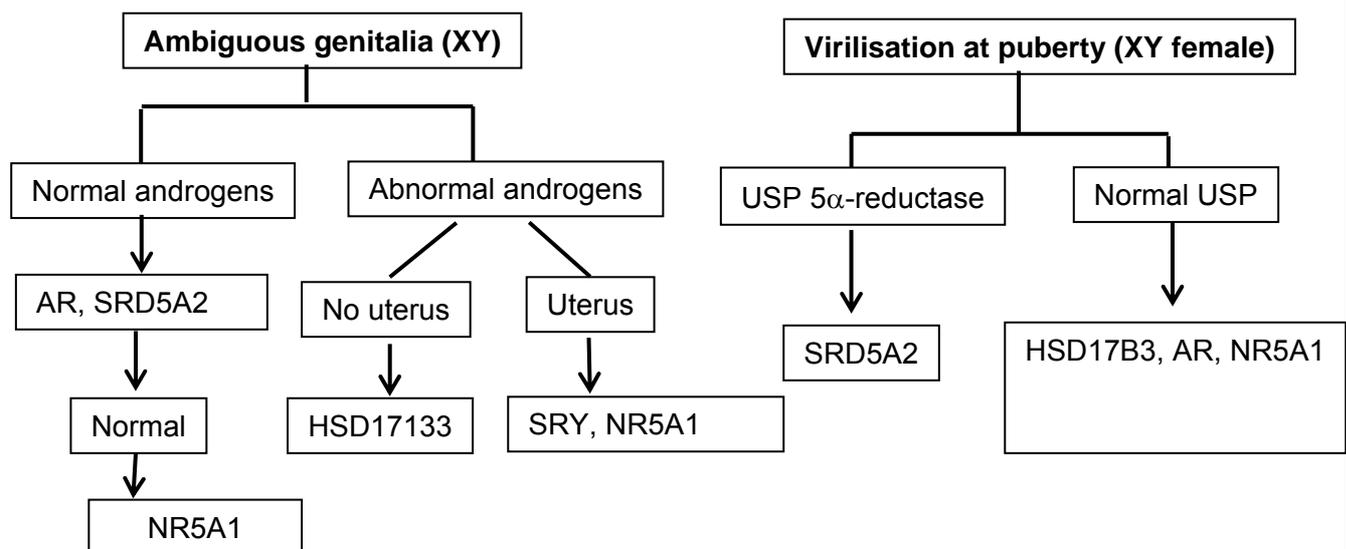
The *clinical validity* of a genetic test is a measure of how well the test predicts the presence or absence of the phenotype, clinical condition or predisposition. It is measured by its *positive predictive value* (the probability of getting the condition given a positive test) and *negative predictive value* (the probability of not getting the condition given a negative test).

As in 25.

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.

The clinical entry point would be abnormal genitalia at birth with biochemical/imaging tests suggestive of gonadal dysgenesis. If there is evidence of adrenal insufficiency, this would raise the stakes for a mutation. At an older age, problems occurring at puberty with virilisation of an XY child raised female would be the clinical entry point. How analysis of NR5A1 may inter-relate with testing other genes is illustrated in the flow diagram.



NB: Increasingly, it is becoming evident that NR5A1 should be tested early in the investigation pathway.

CLINICAL UTILITY	
28. How will the test add to the management of the patient or alter clinical outcome?	Establishing a specific diagnosis is important in XY DSD. This provides data for genetic counselling and decisions on sex assignment (this has life-long implications). Gonadal tumour risk is gene-mutation dependent (high in SRY and probably NR5A1 mutations, low in HSD17B3, SRD5A2). This in turn informs decisions about gonadectomy and its timing. There is a risk of life-threatening adrenal insufficiency associated with an NR5A1 mutation. The management and clinical outcome implications are self-evidence in this context.
29. How will the availability of this test impact on patient and family life?	Families want to have a diagnosis. Especially important in XY DSD where the cause is still unknown in at least 40% of cases. NR5A1 analysis will improve that yield.
30. Benefits of the test	Please provide a summary of the overall benefits of this test.
	Diagnosis, accurate genetic counselling, appropriate sex assignment, tumour risk.
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.
	The indirect tests are too non-specific; currently will result in defining a general category of gonadal dysgenesis.
32. Please describe any specific ethical, legal or social issues with this particular test.	
	None that is different to testing for other candidate genes in DSD.
33. The Testing Criteria must be completed where Testing Criteria are not already available.	
If Testing Criteria are available, do you agree with them	Yes/No
If No:	
Please propose alternative Testing Criteria AND please explain here the reasons for the changes.	
34. Savings or investment per annum in the diagnostic pathway based on national expected activity, cost of diagnostics avoided and cost of genetic test.	
Please show calculations.	
	Avoid a step-wise analysis of other candidate genes. For example, analysing AR, HSD17B3 and SRD5A2 would be an unnecessary cost of £1300 per patient investigated. A conservative annual saving would be £26,000 (based on 20 patient samples).
	Since the phenotype associated with NR5A1 mutations can be so variable, the flow diagram in box 27 is a suggested outline that will at least target those 46, XY DSD genes where mutations are associated with a more specific phenotype.
	Consequently, analysing AR, HSD17B3 and SRD5A2 when not supported by adequate phenotyping (clinical and biochemical) would generate an unnecessary cost of £1300 per patient investigated. An estimated annual saving would be £65,000.

35. List the diagnostic tests/procedures that would no longer be required with costs	
Costs and type of imaging procedures: Pelvic US and MRI	£1200
Costs and types of laboratory pathology tests: Hormone analyses (other than molecular/cyto genetic proposed in this gene dossier)	£ 500
Costs and types of physiological tests (e.g. ECG) N/A	
Cost and types of other investigations/procedures (e.g. biopsy): Occasional biopsy	£ 400
Total cost tests/procedures no longer required	£2100
36. REAL LIFE CASE STUDY	
In collaboration with the clinical lead, describe a <u>real</u> case example to illustrate how the test would improve patient experience.	
<p>A 14 year old girl started to virilise at puberty. Investigations showed a 46, XY karyotype and testosterone was elevated, increasing further with HCG stimulation. The differential included partial androgen insensitivity syndrome, 5α-reductase deficiency and 17β-hydroxysteroid dehydrogenase deficiency. A likely genetic cause was strengthened by her 12 year old sister also have a 46, XY karyotype. Several urinary steroid analyses were performed, numerous imaging studies to identify the site of gonads and the internal genital anatomy. Sequencing of the AR, SRD5A2 and HSD17B3 genes was normal. During the investigative period extending over 18 months, clinical management was a challenge to control the effects of virilisation which can be irreversible (eg, voice deepening, jaw enlargement). Analysis of the NR5A1 gene revealed a heterozygous point mutation (Gln329X) in exon 5 resulting in a premature stop codon. There was now a specific diagnosis and explanation for virilisation in 2 affected sisters. Both are at risk of adrenal insufficiency; assessment of adrenal reserve by ACTH stimulation is currently normal but will need to be monitored regularly.</p>	
37. For the case example, if there are cost savings, please provide these below:	
Figures are based on cost savings for both affected sisters.	
PRE GENETIC TEST	
Costs and type of imaging procedures – US, MRI	2000
Costs and type of laboratory pathology tests – USP, plasma steroids (other than molecular/cyto genetic proposed in this gene dossier)	3000
Costs and type of physiological tests (e.g. ECG)	
Cost and type of other investigations/procedures (e.g. biopsy) - gonads	1200
Cost outpatient consultations (genetics and non genetics)	2600
Total cost pre genetic test	£8800
POST GENETIC TEST	
Costs and type of imaging procedures	
Costs and types laboratory pathology tests – monitoring steroid levels (other than molecular/cyto genetic proposed in this gene dossier)	600
Cost of genetic test proposing in this gene dossier – Carrier detection	300
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)	1200
Total cost post genetic test	£2100
38. Estimated savings for case example described £7000 approximately	

UKGTN Testing Criteria

Approved name and symbol of disease/condition(s): 46,XY Sex Reversal 3; SRXY3	OMIM number(s): 612965
Approved name and symbol of gene(s): nuclear receptor subfamily 5, group A, member 1 NR5A1	OMIM number(s): 184757

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.
Clinical geneticist	<input type="checkbox"/>
Endocrinologist (paediatric/adult)	<input type="checkbox"/>
	<input type="checkbox"/>
	<input type="checkbox"/>

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	Tick if this patient meets criteria
46,XY karyotype AND	<input type="checkbox"/>
evidence of gonadal dysgenesis (uterus, ↑FSH, low testosterone, low AMH, gonadal histology if available).	<input type="checkbox"/>
At risk family members where familial mutation is known	<input type="checkbox"/>

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