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

Test – Disease – Population Triad

Disease – name and description (please provide any alternative names you wish listed) (A)-Testing Criteria	Wilms tumour Wilms tumour, or nephroblastoma, is an embryonal tumour of the kidney and can occur sporadically or in the context of a positive family history. Wilms tumours can occur in isolation or as part of a syndrome where the tumour occurs in association with other clinical features. The diagnosis of isolated Wilms tumour is only made after thorough history, examination and investigation has excluded a syndromic association.
OMIM number for disease	Wilms tumour associated with 11p15 defects is not yet listed on OMIM
Gene – name and description (please provide any alternative names you wish listed)	H19 (ASM1) IGF2 (somatamedin A)
OMIM number for Gene	H19- 103280 IGF2- 147470
Mutational spectrum for which you test	● hypermethylation of H19 ● duplication of paternally inherited 11p15 region ● paternal uniparental disomy of 11p15 region ● maternal H19 DMR microdeletion
Technical Method (s)	1. Methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) 2. 11p15 microsatellite analysis to confirm uniparental disomy in positive cases identified by MS-MLPA 3. Methylation-specific high resolution melt analysis as back-up confirmation for MS-MLPA
Validation Process **Note please explain how this test has been validated for use in your laboratory)**	We have validated the use of the assays through the blinded analysis of a “test set” of 51 samples (24 normal and 27 abnormal). All samples were identified correctly (Scott et al 2008, attached) Analysis has subsequently been extended to include a total of 200 normal control individuals. We are yet to observe a false positive result. This validation work has been carried out in Prof Rahman’s laboratory at ICR, Sutton. Our analyses indicate that MS-MLPA assay is capable, in a single experiment, of detecting all of the 11p15 epigenetic and copy number defects recognised in overgrowth and growth retardation orders. Unlike the existing assays of methylation in the region, it differentiates heritable copy number abnormalities from isolated methylation defects. In addition, the use of MS-MLPA as a first-line assay limits the need for microsatellite analysis to the small number identified with probable UPD. Compared with existing diagnostic testing approaches, this approach therefore both broadens the range of detectable 11p15 abnormalities and reduces the complexity and cost of analysis of the region. In addition we are currently validating the use of a second method (MS-HRM) in the diagnostic lab for confirming positive cases detected by MS-MLPA and for fails.

Are you providing this test already? If yes, how many reports have you produced? **NB please give the number of mutation positive/negative samples you have reported**	No
For how long have you been providing this service?	Not applicable
Is there specialised local clinical/research expertise for this disease?	**Yes** (circled) **No** **Please provide details** There is both clinical and research expertise locally as Professor Rahman, whose group (the Childhood Overgrowth (COG) Study) at the nearby Institute of Cancer Research optimised the 11p15 MS-MLPA, is also an Honorary Consultant at St George's. Dr Kate Tatton Brown also has extensive clinical and research expertise in the area of overgrowth.
Are you testing for other genes/diseases closely allied to this one? Please give details	SW Thames Regional Molecular Genetics Diagnostic Laboratory is currently offering NSD1 testing for Sotos syndrome, another overgrowth condition. In addition, the COG study aims to identify novel overgrowth genes and their associated phenotypes. It is envisaged that tests for novel genes, shown to be significant contributors to human overgrowth, will also be offered in the St George's laboratory in the future.
Your Activity How many tests do you (intend to) provide annually in your laboratory?	Approximately 20 tests
Based on experience how many tests will be required nationally? Please identify the information on which this is based	Approximately 20 tests. Information based on number of tests performed in laboratories that are offering testing for these conditions by different techniques.

Epidemiology

Estimated prevalence of disease in the general UK population Please identify the information on which this is based	1 in 10,000 (Stiller et al 1990) 11p15 defects are present in 5% of cases, the majority of whom present with isolated Wilms tumour (paper submitted / personal communication N Rahman).
Estimated gene frequency (Carrier frequency or allele frequency) Please identify the information on which this is based	No population-based data are available. Based on data from disease-based studies (above), it is estimated that the frequency of 11p15 defects in the general population is 1 in 10,000 – 20,000.
Estimated penetrance Please identify the information on which this is based	Large numbers of individuals have been tested for the 11p15 defects associated with overgrowth over the last 10-15 years. The accumulated data suggest that the 11p15 defects have a penetrance approaching 100% (Weksberg et al 2006). However, 11p15 defects have only recently been identified as a cause of isolated Wilms tumour. Currently data is therefore not available for the proportion of individuals with a constitutional 11p15 defect who develop Wilms tumour. However, individuals with BWS and a Wilms tumour associated 11p15 defect (eg H19 hypermethylation, pat UPD11 or duplication of the paternal allele) have approximately 13% chance of developing Wilms tumour (Cooper et al).
Target Population The essential clinical or family history features defining the target population must be described. (C)-Testing Criteria	Individuals with Wilms tumour.
Estimated prevalence of disease in the target population	See prevalence in general population box

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

Please tick the relevant clinical management criteria that this test effects.	**YES**	**NO**
Diagnosis	√	
Treatment		√
Prognosis & Management	√	
Presymptomatic testing	√	
Risk Assessment	√	

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.	The validation data presented above indicate that the MS-MLPA test has analytical sensitivity and specificity approaching 100%.
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) *Positive predictive value* and *penetrance* are notionally equivalent for any single genetic allele – the probability of developing disease given a positive test. The relationship is much more complex if more than one gene is responsible for the disease (locus heterogeneity), or if in any one gene there are multiple alleles (allelic heterogeneity), unless all the alleles are tested. In these cases, there are implications for the *clinical sensitivity* of the test and for *its negative predictive value*. For example, for a disease (such as APKD) that may be caused by either of two separate genes, even if each is 100 percent penetrant, the *clinical sensitivity* and the *negative predictive value* (and *clinical validity*) will both be reduced: *clinical sensitivity* since its maximum value can be no greater than the proportion of the disease that is caused by that particular gene, and *negative predictive value* since a negative test on Gene A will be no guarantee that the patient will not develop the phenotype, because the disease may be caused by Gene B. A similar form of analysis may be applied to genes with multiple alleles unless the "test" measures all the alleles	**Clinical Sensitivity** The test is capable of detecting all 11p15 defects reported in patients with Wilms tumour. Clinical sensitivity is therefore estimated at 5%, including all cases with reported 11p15 defects. **Clinical Specificity** The validation data presented above indicate that the test has clinical specificity approaching 100%.

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). The denominator in this case is the number of people with a positive or a negative test respectively - not the number with or without the disease. The clinical validity may be calculated knowing the sensitivity and the specificity and the prevalence of the disease in the population being studied. Positive and negative predictive values depend critically on the prevalence of the disease in the test population *Positive predictive value* and *penetrance* are notionally equivalent for any single genetic allele – the probability of developing disease given a positive test. The relationship is much more complex if more than one gene is responsible for the disease (locus heterogeneity), or if in any one gene there are multiple alleles (allelic heterogeneity), unless all the alleles are tested. In these cases, there are implications for the *clinical sensitivity* of the test and for *its negative predictive value*. For example, for a disease (such as APKD) that may be caused by either of two separate genes, even if each is 100 percent penetrant, the *clinical sensitivity* and the *negative predictive value* (and *clinical validity*) will both be reduced: c*linical sensitivity* since its maximum value can be no greater than the proportion of the disease that is caused by that particular gene, and *negative predictive value* since a negative test on Gene A will be no guarantee that the patient will not develop the phenotype, because the disease may be caused by Gene B. A similar form of analysis may be applied to genes with multiple alleles unless the "test" measures all the alleles.	**Positive predictive value / penetrance** Published data indicate that 11p15 defects detectable with the test may be fully penetrant and have a positive predictive value approaching 100%. **Negative predictive value** Not applicable. 11p15 analysis is used principally to confirm diagnosis and/or to inform offspring/recurrence risks and estimate Wilms tumour risk rather than to rule out an underlying diagnosis (see clinical utility section). In the case of a negative test result, patients/families are counselled according to empiric risks for individuals in their phenotypic group with normal 11p15 status.

Clinical utility of test in target population (Please refer to Appendix A) Please provide a full description of the clinical care pathway for those individuals undergoing testing. This should include details of which medical specialties will be able to refer for testing. (B)-Testing Criteria How will the test add to the management of the patient or alter clinical outcome? 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 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 Are there specific ethical, legal or social issues with this test?	**<u>Testing criteria</u>** *Individuals with Wilms tumour.* **<u>Referring clinicians</u>** Clinical Geneticist (consultant or specialist registrar) Consultant Paediatrician **<u>Outcome</u>** Abnormality detected a. Molecular predisposition to tumour development identified b. If case presents with a unilateral Wilms tumour, identification of a germline 11p15 defect will prompt appropriate screening for the second, at risk, kidney. b. MS-MLPA distinguishes heritable from non-heritable 11p15 defects and enables accurate estimation of recurrence and offspring risks. No abnormality detected Where there is a known heritable 11p15 defect in a family, a negative test result in an 'at-risk' relative allows the reassurance and appropriate counselling of the patient and the avoidance of unnecessary surveillance. There are no ethical, legal or social issues specific to this test.

Please complete the referral pathway diagram on the following page and the testing criteria form.

Referral Pathway Template –

NOTE: Please use this page as a template. Please expand the test boxes manually as needed.

TARGET POPULATION

Individuals with Wilms tumour.

WHAT TYPE AND LEVEL OF PROFESSIONAL OR REFERRER DO YOU ACCEPT SAMPLES FROM?

1. Clinical Genetics- Consultant and Specialist registrar
2. Consultant Paediatric oncologists

PLEASE PROVIDE DETAILS OF HOW REFERRALS WILL BE ASSESSED FOR APPROPRIATENESS?

Testing criteria will be advertised on UKGTN website. After one year the service will be audited with referring clinicians contacted. The types of cases being referred will be analysed and criteria amended if appropriate.

HOW MANY TESTS DO YOU EXPECT TO PERFORM ANNUALLY?

20

UKGTN 'Testing criteria' template

UK Genetic Testing Network

Name of Disease(s): WILMS TUMOR 1; WT1 (194070)

Name of gene(s):
H19, imprinted maternally expressed transcript - H19 (103280)
insulin-like growth factor 2 (somatomedin A) - IGF2 (147470)

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:
(Please indicate with a tick which category refers to the referrer).

Referrer	Tick if this refers to you.
Clinical Geneticist	
Consultant Paediatric oncologists	

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

Criteria	Tick if this patient meets criteria
Individual with Wilms tumour	

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.