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

Test – Disease – Population Triad

Disease – name	Achondrogenesis type II and hypochondrogenesis
OMIM number for disease	200610
Disease – alternative names please provide any alternative names you wish listed	
Disease – please provide a brief description of the disease characteristics	The most severe disorders in the type II collagenopathy spectrum, achondrogenesis and hypochondrogenesis are perinatally lethal and present early in the first or second trimester of pregnancy with severe shortening of the long bones, abnormal ossification and hydrops. There are characteristic radiographic abnormalities, usually detected as part of perinatal pathology investigation.
Disease - mode of inheritance	New dominant mutations
Gene – name(s)	*COL2A1*
OMIM number for gene(s)	120140
Gene – alternative names please provide any alternative names you wish listed	*Chondrocalcin* (120140)
Gene – description(s) (including number of amplicons).	54 exons, to be PCR amplified in 55 amplicons.
Mutational spectrum for which you test including details of known common mutations.	• Most mutations occur in the triple helical domain. • No mutation hot-spots exist and there are few recurrent mutations.
Technical Method (s)	PCR amplification from extracted DNA of all coding exons, including splice sites, followed by fluorescent unidirectional sequencing on ABI 3730.
Validation Process Note: please explain how this test has been validated for use in your laboratory	PCR amplification, followed by unidirectional sequencing, is applied to a number of genes in our laboratory. In a collaborative CMGS study (Ellard et al) in which we participated, this was shown to have a sensitivity of >99%.
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**	**No** **If Yes:** **Number of reports issued:** **Number of reports mutation positive:** **Number of reports mutation negative:**

For how long have you been providing this service?	**N/A**
Is there specialised local clinical/research expertise for this disease?	**Yes** [ ] **Please provide details** The affiliated clinical genetics department offer combined, multidisciplinary clinical services in both skeletal dysplasia and fetal medicine, receiving tertiary referrals from the South East region. The existing diagnostic and management skills will provide expertise to support the molecular service.
Are you testing for other genes/diseases closely allied to this one? Please give details	Gene dossier simultaneously resubmitted for testing of other *COL2A1*-related disorders and for investigation of other types of skeletal dysplasia with prenatal and early infantile onset –ie thanatophoric dysplasia and achondroplasia
Your Current Activity If applicable - How many tests do you currently provide annually in your laboratory?	Index cases: Family members where mutation is known:
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: 10 Family members where mutation is known: N/A
Based on experience how many tests will be required nationally (UK wide)? Please identify the information on which this is based	10 Family members where mutation is known: N/A
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 are not aware of a UK laboratory offering this test as a prenatal mutation screen. Addenbrookes offers COL2A1 molecular analysis postnatally.

Epidemiology

Estimated prevalence of disease in the general UK population Please identify the information on which this is based	1 in 100,000 Medical literature recorded observation
Estimated gene frequency (Carrier frequency or allele frequency) Please identify the information on which this is based	All new dominant mutations
Estimated penetrance Please identify the information on which this is based	100%
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)	Fetuses with short long bones (<<3rd c.) with onset in the late first or early second trimester with hydrops
Estimated prevalence of disease in the target population	Up to 50%

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.	Analytical Sensitivity >99% Analytical Specificity >99%
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: 50-80% 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 – 100% NPV – 0%
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.	

Clinical utility of test in target population Please provide a description of the clinical care pathway.	This testing service will allow accurate genetic counselling in the event of short long bone detection on fetal ultrasound imaging. Where the condition is deemed severe enough to interrupt the pregnancy a couple may seek to terminate the pregnancy and this test will help the decision making process of all involved. It will also aid perinatal investigations into the cause of severe long bone shortening after *post mortem* examination.
How will the test add to the management of the patient or alter clinical outcome?	Use of this test will be of benefit to genetic counselling, diagnosis, prognostication and management in the event of prenatal detection of short fetal long. Couples will have additional, valuable medical information to aid decision-making and it will inform decisions to embark upon future pregnancies.
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.	The obvious impact this test will have is to help couples make decisions when faced with possible recurrence of a severe disorder. Other types of achondrogenesis represent homozygous mutations in different genes with a 1 in 4 risk of recurrence; the risk is <1% in type II achondrogenesis. The test will negate the need for serial US scans and it will aid diagnosis by the perinatal pathologist. Cases of achondrogenesis referred to the skeletal dysplasia service by pathologists have had extensive histological examination and radiographic opinions sought from a number of radiologists, often without consequent clarification of the recurrence risks.
What are the consequences of not doing this genetic test. Commissioners have asked for specific information to support introduction of tests.	Inaccurate genetic counselling Inappropriate monitoring during subsequent pregnancies, either too much or too little surveillance, depending upon the exact type of achondrogenesis.
Utility of test in the NHS In a couple of sentences explain the utility of this test for the disease(s)	This test is of value in helping couples decide how to proceed with a pregnancy in the event of antenatal detection of extremely short fetal long bones. It adds a valuable diagnostic dimension to the counselling situation.
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	Postnatally a clinical and radiographic examination will usually make the diagnosis, but it may be difficult clinically to differentiate between this and other types of ahondrogenesis on clinical and radiographic grounds. Since these other types of achondrogenesis have a different risk of recurrence, molecular testing provides valuable, additional information.
Please describe any specific ethical, legal or social issues with this particular test?	

UKGTN Testing criteria

Name of Disease(s): ACHONDROGENESIS, TYPE II; ACG2 (200610)

Name of gene(s): collagen, type II, alpha 1; COL2A1 (120140)

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	
Perinatal Pathologist	

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

Criteria	Tick if this patient meets criteria
Characteristic postnatal radiographic features (if delivered): • underossified vertebral bodies • unossified pubic and ischial bones • small iliac bones • short tubular bones with metaphyseal cupping lateral bowing of femora • short ribs	

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.

Approval Date: Sept 2010 Submitting laboratory: GSTS Pathology, Guy's Hospital