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

Test – Disease – Population Triad

Disease – name	Carpenter syndrome
OMIM number for disease	201000
Disease – alternative names please provide any alternative names you wish listed	Acrocephalopolysyndactyly type II, ACPS II
Disease – please provide a brief description of the disease characteristics	The characteristic manifestations are craniosynostosis (primarily of the metopic and sagittal sutures), obesity, polydactyly and soft tissue syndactyly. Other well recognised characteristics include brachydactyly with shortening or absence of the middle phalanges, molar agenesis, genu valgum, hypogenitalism, congenital heart defects, umbilical hernia and learning disability.
Disease - mode of inheritance	Autosomal recessive
Gene – name(s)	RAS-ASSOCIATED PROTEIN RAB23; RAB23
OMIM number for gene(s)	606144
Gene – alternative names please provide any alternative names you wish listed	
Gene – description(s) (including number of amplicons).	*RAB23* is located on 6p12.1 and is encoded by 7 exons, only 6 of which are coding (exons 2-7 are screened in 6 amplicons). The cDNA encodes a 237 amino acid vesicle transport protein that is essential for neuromuscular synaptogenesis. RAB23 is 30 to 35% identical to other mammalian Rab proteins and includes all the canonical motifs required for guanine nucleotide binding, GTP hydrolysis, membrane association, and the conformational switch between the GTP and GDP-bound state. The expression pattern of *RAB23* RNA is similar to that of *GLI3* (165240), another negative regulator of the Shh signaling pathway.
Mutational spectrum for which you test including details of known common mutations.	Nonsense mutations, small insertions, deletions and splicing mutations resulting in premature termination of translation. Missense mutations also occur. Exon 5 contains a common founder mutation, p.Leu145X, which is present in individuals of north European descent.
Technical Method (s)	Bidirectional fluorescent sequencing.
Validation Process Note: please explain how this test has been validated for use in your laboratory	Bidirectional fluorescent sequencing is used by our laboratory for mutation scanning of several genes including the craniofacial genes *FGFR1, FGFR2, FGFR3, TWIST1* and *EFNB1.* Prior to use all primers were checked for SNPs and 2 normal controls sequenced to confirm specific amplification. Confirmation of known mutations using controls from Professor Wilkie was also carried out.
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 – since May 2008 we have issued 4 reports: 1 compound heterozygote confirmation of mutations identified in a research laboratory, and 3 family tests including 1 prenatal (all heterozygous). Mutation screening has been undertaken to date in Prof Wilkie's

	laboratory. Of 26 samples tested, 8 were found to be positive for *RAB23* mutations (31%), and 3 were found to have deletions that included the *GLI3* gene (11%). The *RAB23* service is due to transfer to the diagnostic laboratory in 2010. We already offer a dosage test for *GLI3*.
For how long have you been providing this service?	18 months
Is there specialised local clinical/research expertise for this disease?	**Yes ✓** | **No** | **Please provide details** Professor Andrew Wilkie's research group at the Weatherall Institute of Molecular Medicine was the first to identify *RAB23* mutations in Carpenter syndrome. In addition his laboratory has worked on many of the craniofacial genes. An NCG funded referral centre for craniofacial disorders is based at the John Radcliffe, Oxford, with weekly clinics for patients. The lead clinician is Mr Steve Wall.
Are you testing for other genes/diseases closely allied to this one? Please give details	Yes – *FGFR1, FGFR2, FGFR3, TWIST1, EFNB1, ALX4, MSX2, RUNX2.* These are all genes involved in craniofacial development. We also test for a number of skeletal genes, including *GLI3, ROR2, HOXD13, TCOF1* and *FLNA*.
Your Activity If applicable - How many tests do you currently provide annually in your laboratory?	Index cases: 0 Family members where mutation is known: 2
Your Activity 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: at least 3 Family members where mutation is known: at least 2
Based on experience how many tests will be required nationally (UK wide)? Please identify the information on which this is based	Index cases: approx 3 Family members where mutation is known: approx 2 Number of index cases is based on a disease incidence of 1 per million live births and a detection rate of 31% amongst clinical referrals.
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 provide a national and international service. Currently, however, NCG funding covers patients from all of the UK. We are not aware of any other UK laboratory offering this analysis.

Epidemiology

Estimated prevalence of disease in the general UK population Please identify the information on which this is based	Based on the number of known cases in the United States the disease prevalence is estimated at 1 per 1 million live births.
Estimated gene frequency (Carrier frequency or allele frequency) Please identify the information on which this is based	As this is an autosomal recessive disease the carrier frequency is estimated at 1 in 500 based on the incidence given above. The above is based on a gene frequency of 1 in 1000 equating from disease incidence is 1 in 100,000
Estimated penetrance Please identify the information on which this is based	Penetrance is 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)	1. Individuals with a clinical diagnosis of Carpenter syndrome associated with the following features: - autosomal recessive inheritance pattern - craniosynostosis - digital malformation - obesity 2. Relatives of individuals with identified mutations
Estimated prevalence of disease in the target population	*RAB23* mutations are expected to account for about 31% of cases with craniosynostosis and polysyndactyly.

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. If more than one gene will be tested, please include your testing strategy and data on the expected proportions of positive results for each part of the process. Please illustrate this with a flow diagram.	Bidirectional sequencing is expected to have a sensitivity approaching 100%, as no whole exon deletions or duplications have been reported to date. The specificity is also expected to be high, as the majority of the reported mutations are truncating mutations. Missense mutations are identified, but the gene is highly conserved across species and paralogues.
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 specificity approaches 100% as homozygous mutations in *RAB23* are fully penetrant. Clinical sensitivity in Carpenter syndrome demonstrating classical clinical features is over 90%. In subjects with relaxed criteria for diagnosis (craniosynostosis and polysyndactyly), sensitivity is ~31%. In these cases there is some clinical overlap with Greig syndrome, for which we also offer testing.
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).	Positive predictive value approaches 100% in probands and affected relatives.

Clinical utility of test in target population (Please refer to Appendix A) Please provide a description of the clinical care pathway.	Main benefits of a positive test result are: - To provide a definitive diagnosis - To ensure appropriate life-transforming investigations and treatment of congenital heart disease and hydrocephalus. Echocardiography and brain MRI would be indicated in the event of a positive result. - For suitable prognostic and family-planning advice. Target population: – individuals with a suspected clinical diagnosis of Carpenter syndrome with the features identified previously – relatives of individuals with identified RAB23 mutations Referrals are expected from clinical geneticists. All referrals will be assessed for appropriateness through the established NCG craniofacial clinical review process. Testing will not be carried out until appropriate clinical details have been received.
How will the test add to the management of the patient or alter clinical outcome?	A positive result will trigger investigations for craniosynostosis, heart and renal malformations, if not previously performed. Accurate prediction of recurrence risk can be given to relatives, and carrier and prenatal testing offered if appropriate.
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?	A positive result will avoid pursuit of other genetic investigations, for example mutations in *GLI3*.
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
Please describe any specific ethical, legal or social issues with this particular test?	Prenatal testing may identify unaffected carriers.

UKGTN Testing criteria

Name of Disease(s): CARPENTER SYNDROME (201000)

Name of gene(s): RAB23, member RAS oncogene family; RAB23 (606144)

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	

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

Criteria	Tick if this patient meets criteria
Craniosynostosis of the metopic or sagittal sutures **AND**	
Polydactyly and/or syndactyly of hands/feet	

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: Oxford Molecular Genetics