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

TEST – DISEASE/CONDITION – POPULATION TRIAD			
Submitting laboratory:	**Cardiff 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)	Parkinson Disease 7 PARKINSON DISEASE 7, AUTOSOMAL RECESSIVE EARLY-ONSET; PARK7		
2. OMIM number for disease/condition	606324		
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.	Parkinson Disease 7 is a typically early onset Parkinsonism that is often clinically indistinguishable from idiopathic PD. Patients present before 40 years of age with resting tremor, muscle rigidity and slowed movement (bradykinesia). The disease shows slow progression and a good response to L-dopa.		
4. Disease/condition – mode of inheritance	Autosomal recessive		
5. Gene – approved name(s) and symbol as published on HUGO database (alternative names will be listed on the UKGTN website)	Parkinson protein 7; PARK7		
6. OMIM number for gene(s)	602533		
7. Gene – description(s)	The PARK7 gene is mapped to chromosome 1p36.23 and contains 8 exons. The first two exons, 1A and 1B are non-coding and are alternatively spliced. The 8 exons span 24 kb and encode a 189 amino acid protein. AGREE		
7b. Number of amplicons to provide this test	6 amplicons (exons 2-7)		
7c. MolU/Cyto band that this test is assigned to	MolU band D 2012/13 GenU band E 2013/14		
8. Mutational spectrum for which you test including details of known common mutations	Screening for point mutations and deletions/duplications in the 6 coding exons of the PARK7 gene.		
9. Technical method(s)	Sequencing analysis of the 6 coding exons of the PARK7 gene and MLPA analysis of exons 3, 5 and 7 as well as the 5' UTR immediate to exon 1 of the PARK7 gene.		
10. Validation process Please explain how this test has been validated for use in your laboratory	Laboratory validation of probe sequences (SNP checking) and use of correct reference sequences to ensure that the appropriate sequence is analysed. MLPA assay further validated using known normal and mutation controls.		
11a. Are you providing this test already?	No		
11b. If yes, how many reports have you produced?			
11c. Number of reports mutation positive			
11d. Number of reports mutation negative			
12. For how long have you been providing this service?	Currently in final stages of validation		

13a. Is there specialised local clinical/research expertise for this disease?	Yes
13b. If yes, please provide details	Dr. Huw Morris, Senior Lecturer in Neurology is engaged in a clinical epidemiological project on young onset Parkinson's disease and is carrying out research into the genetics of young onset Parkinson's disease. He will assist with review of requests and reports as required.
14. Are you testing for other genes/diseases/conditions closely allied to this one? Please give details	Yes – We also provide a screening service for the PARK2 gene, implicated in early onset autosomal recessive PD, point mutation analysis for the common LRRK2 gene mutations implicated in autosomal dominant adult onset PD and will be submitting a gene dossier for a PINK1 (PARK6) screening service implicated in autosomal recessive PD.
Your current activity If applicable - How many tests do you currently provide annually in your laboratory?	n/a
15a. Index cases	n/a
15b. Family members where mutation is known	n/a
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?	
16a. Index cases	200
16b. Family members where mutation is known	~10
Based on experience how many tests will be required nationally (UK wide) per annum? Please identify the information on which this is based	We currently provide approximately 50 tests per year for PARK2. One other laboratory currently provides PARK2 testing in the UK. Assuming that they receive a similar number of requests and have a similar pick up rate (20%) it is anticipated that around 80 patients may then proceed to PINK1 & PARK7 analyses. It is our intension to run both PINK1 and PARK7 analyses in tandem given their gene frequencies.
17a. Index cases	80
17b. Family members where mutation is known	~10
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".	Full national need can be provided.

EPIDEMIOLOGY

19. Estimated prevalence of condition in the general UK population Please identify the information on which this is based	Prevalence early onset Parkinson's disease = 10/100,000 (age at onset <45) = 5000 in UK Incidence early onset Parkinson's disease 1/100,000/year = 500/year UK Schrag et al BMJ. 2000 Jul 1;321(7252):21-2 Van den Eeden Am J Epidemiol. 2003 Jun 1;157(11):1015-22.
20. Estimated gene frequency (Carrier frequency or allele frequency) Please identify the information on which this is based	Unknown
21. Estimated penetrance Please identify the information on which this is based	Literature suggests that Parkinson Disease 7 is fully penetrant and inheritance of two PARK7 mutations confirms the carrier will develop early onset PD. Abou-Sleiman et al. Ann of Neurol 2003; 54(3): 283 Annesi et al. Ann Neurol 2005;58:803–807 Bonifati et al. Science 2003; 299: 256-259
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.	The test is indicated for patients with young onset PD and patients in PD families showing an autosomal recessive inheritance pattern. The prevalence of PARK7 related PD is estimated to be between 1% and 3.6% as indicated by the data available. Mutations are not population specific. Ibanez et al. (2003) Neurology; 61:1429–1431 Abou-Sleiman et al. Ann of Neurol; 54(3): 283–286

INTENDED USE

23. Please tick the relevant clinical purpose of testing		
Diagnosis	☑ **Yes**	☐ **No**
Treatment	☐ **Yes**	☑ **No**
Prognosis & management	☐ **Yes**	☑ **No**
Presymptomatic testing	☑ **Yes**	☐ **No**
Carrier testing for family members	☑ **Yes**	☐ **No**
Prenatal testing	☐ **Yes**	☑ **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.

Analytical sensitivity and specificity of sequencing and MLPA analyses for germline mutations is >99%. However our current MLPA assay lacks probes for 3 coding and 1 non coding exon.

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).

There is considerable genetic heterogeneity in familial and young onset Parkinson's disease. The "gold standard" for diagnosis is the application of the Queen Square brain bank clinical diagnostic criteria which have been shown to have a high correlation with post-mortem pathology. The primary aim of genetic testing in PD is to delineate the inheritance of the disease.

Clinical sensitivity
PARK7 – 1-3.6% of young onset disease

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).

Approximately 10% of Parkinson's disease in the UK is genetic. However a positive genetic test has extremely high predictive value for individual cases and their families; this is particularly true where onset is before the age of 50 years. 1% to 3.6% of early onset will be positive and 100% predictive value.

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.

See attached sheet.

CLINICAL UTILITY

28. How will the test add to the management of the patient or alter clinical outcome?

The main role of PARK7 testing will be in enabling accurate genetic counselling.

Although Parkinson's disease is usually a clinical diagnosis in the younger age group there may be uncertainty between a diagnosis of Parkinson's disease or dopa responsive dystonia. This has implications for response to treatment and the development of treatment related complications (DRD patients do not develop treatment related complications).

29. How will the availability of this test impact on patient and family life?

Young onset Parkinson's disease may be due to autosomal recessive or autosomal dominant disease. The identification of two PARK7 mutations will allow appropriate genetic counselling for individuals with early onset Parkinson's disease. Information on prognosis, and might lead to the commencement of treatment in cases of PD that are initially suspected to be psychogenic.

30. Benefits of the test Please provide a summary of the overall benefits of this test.

There are at least 12 genes for monogenic forms of PD identified to date. Identification of two PARK7 mutations will abrogate the need for further genetic investigations and will enable carrier testing for at risk relatives.

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.

There are no alternative means of diagnosing PARK7 related Parkinson's disease other than molecular diagnosis.

32. Please describe any specific ethical, legal or social issues with this particular test.

None

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.

35. List the diagnostic tests/procedures that would no longer be required with costs. E

In addition to PARK2, PINK1 and PARK7, autosomal recessively inherited early onset Parkinsonism is also attributed to PARK9 (ATP13A2) for which we currently do not offer testing. Furthermore, patients confirmed to have PARK7 associated Parkinson disease would not be screened for mutations in novel genes as the discovery of Parkinson disease loci continues.

The differential diagnosis of Early Onset Parkinsonism-Dystonia includes Wilson's disease, Dopa-Responsive dystonia and Pallido-pyramidal syndromes such as Kufor-Rakeb syndrome and SPG-11, PLA2G6 and FBXO7 related disease. Further tests that might be needed to diagnose these conditions include T2* MRI imaging, CSF neurotransmitter analysis, therapeutic trials of L-DOPA, 24 hour urinary copper analysis and neuro-ophthalmological assessment in addition to further genetic analysis (as mentioned above). A positive diagnosis of PARK7 related disease will exclude other differential diagnoses and may avoid the need for further tests.

Costs and type of imaging procedures	
Costs and types of laboratory pathology tests (other than molecular/cyto genetic proposed in this gene dossier)	
Costs and types of physiological tests (e.g. ECG)	
Cost and types of other investigations/procedures (e.g. biopsy)	
Total cost tests/procedures no longer required	**£**

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.

Cannot yet provide real case for PARK7 mutation analysis. The analysis will primarily be useful for the family with regards to genetic counselling.

37. For the case example, if there are cost savings, please provide these below:

There are no cost savings to date. The benefit is often to the family: the knowledge and availability of further testing within the family, rather than financial savings.

PRE GENETIC TEST

Costs and type of imaging procedures	
Costs and type of laboratory pathology tests (other than molecular/cyto genetic proposed in this gene dossier)	
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)	
Total cost pre genetic test	**£**

POST GENETIC TEST

Costs and type of imaging procedures	
Costs and types laboratory pathology tests (other than molecular/cyto genetic proposed in this gene dossier)	
Cost of genetic test proposing in this gene dossier	
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)	
Total cost post genetic test	**£**

38. Estimated savings for case example described

UKGTN Testing Criteria

Approved name and symbol of disease/condition(s):	**OMIM number(s):**
Parkinson Disease 7, Autosomal Recessive Early-Onset; PARK7	606324
Approved name and symbol of gene(s):	**OMIM number(s):**
parkinson protein 7**;** PARK7	602533

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 Neurologist	
Consultant Clinical Geneticists	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
Early onset Parkinson Disease (EOPD) (<45 years) **AND**	
no evidence of autosomal dominant inheritance-**AND**	
PARK2 has been excluded	
At risk family members where familial mutation is known	

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

Pink highlighting indicates the test pathway referred to in this gene dossier