

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

TEST – DISEASE/CONDITION – POPULATION TRIAD	
Submitting laboratory: Newcastle RGC	Approved: Sept 2013
1. Disease/condition – approved name and symbol as published on the OMIM database (alternative names will be listed on the UKGTN website)	BROOKE-SPIEGLER SYNDROME; BRSS TRICHOEPITHELIOMA, MULTIPLE FAMILIAL, 1 CYLINDROMATOSIS, FAMILIAL
2. OMIM number for disease/condition	605041, 601606, 132700
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.	Multiple disfiguring tumours arise on the head, scalp and torso. These tumours, while usually benign, can be extremely painful and distressing. Repeated surgery may be required to reduce tumour burden.
4. Disease/condition – mode of inheritance	AD
5. Gene – approved name(s) and symbol as published on HUGO database (alternative names will be listed on the UKGTN website)	cylindromatosis (turban tumor syndrome); CYLD 2584
6. OMIM number for gene(s)	605018
7. Gene – description(s)	The tumor suppressor CYLD is a deubiquitinating enzyme that removes lys63-linked ubiquitin chains and acts as a negative regulator of NF-kappa-B (see 164011) signaling. CYLD deubiquitinates several NF-kappa-B regulators, including TRAF2 (601895), TRAF6 (602355), and NEMO (IKBKG; 300248), as well as BCL3 (109560), a member of the NF-kappa-B family of transcription factors (Hutti et al., 2009).
7b. Number of amplicons to provide this test	17
7c. MolU/Cyto band that this test is assigned to	Band E
8. Mutational spectrum for which you test including details of known common mutations	98 mutations exist, predominantly affecting the 3' region of the gene that encodes the catalytic region of the CYLD protein
9. Technical method(s)	PCR and sequencing
10. Validation process Please explain how this test has been validated for use in your laboratory	The basic techniques are well established in the Northern Genetics service, and the specific test has been validated in confirming research findings in local patients
11a. Are you providing this test already?	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes
11b. If yes, how many reports have you produced?	30
11c. Number of reports mutation positive	17
11d. Number of reports mutation negative	13

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12. For how long have you been providing this service?	7 years
13a. Is there specialised local clinical/research expertise for this disease?	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes
13b. If yes, please provide details	Dermatology and genetics departments are involved in the management of several families with these conditions
14. Are you testing for other genes/diseases/conditions closely allied to this one? Please give details	No
Your current activity If applicable - How many tests do you currently provide annually in your laboratory?	
15a. Index cases	3
15b. Family members where mutation is known	1
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	10
16b. Family members where mutation is known	30
Based on experience how many tests will be required nationally (UK wide) per annum? Please identify the information on which this is based	
17a. Index cases	8
17b. Family members where mutation is known	15
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".	Not Known

EPIDEMIOLOGY	
19. Estimated prevalence of condition in the general UK population Please identify the information on which this is based	1 in 100000 Rough estimate based on number affected in catchment area.
20. Estimated gene frequency (Carrier frequency or allele frequency) Please identify the information on which this is based	1 in 100000
21. Estimated penetrance Please identify the information on which this is based	Almost 100% Based on studies of 3 local pedigrees with correlation of genotype and phenotype
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.	No less than 50%, as all patients that fulfil the criteria are likely to come from families with <i>CYLD</i> mutations
INTENDED USE	
23. Please tick the relevant clinical purpose of testing n/a to additional provider applications	
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 checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Carrier testing for family members	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Prenatal testing	<input type="checkbox"/> Yes <input checked="" 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.

Sensitivity almost 100%

Specificity almost 100%

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).

Sensitivity 90%

Specificity almost 100%

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).

PPV – and NPV are almost 100% each; the disease is highly penetrant and only a single locus has been identified in linkage studies.

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.

Only one gene to be tested.

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

Genetic counselling of patients that have a family history of *CYLD* mutation carrier status that influence family planning.

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

Presymptomatic diagnostic testing for negative carriers will influence family planning.

30. Benefits of the test

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

CYLD mutation carriers face the prospect of repeated surgery to control tumour burden. Presymptomatic diagnostic testing has been requested in pedigrees known to carry the mutation as this has influenced family planning. The recent discovery of TRK as a therapeutic target in *CYLD* mutation carriers has raised the possibility of a topical therapeutic intervention in mutation carriers. Whilst the benefit of this awaits to be determined in clinical trials, early awareness of mutation status will influence selection for trials, and in the future potential treatment to avoid surgery.

<p>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.</p>										
<p>Histological testing of skin tumours when the condition is apparent. The oldest carrier to present is at 42, which makes genetic testing necessary for family planning if requested by the patient.</p>										
<p>32. Please describe any specific ethical, legal or social issues with this particular test.</p>										
<p>None</p>										
<p>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.</p>										
<p>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.</p>										
<p>The calculation on savings would be influenced by the development of novel non-surgical treatments. The cost of repeated surgery and hospital visits relating to surgery can be significant for patients who undergo operations every 4-6 months. It is hoped that the identification of presymptomatic carriers will allow early treatment with topical agents that inhibit tumour growth. At present, the inhibition of a kinase called TRK appears to be a potential strategy, which will be explored in future clinical trials in <i>CYLD</i> mutation carriers.</p>										
<p>35. List the diagnostic tests/procedures that would no longer be required with costs.</p>										
<p>Not applicable as no proxy diagnostic test for young asymptomatic carriers</p>										
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="padding: 2px;">Costs and type of imaging procedures</td> <td style="width: 50px;"></td> </tr> <tr> <td style="padding: 2px;">Costs and types of laboratory pathology tests (other than molecular/cyto genetic proposed in this gene dossier)</td> <td></td> </tr> <tr> <td style="padding: 2px;">Costs and types of physiological tests (e.g. ECG)</td> <td></td> </tr> <tr> <td style="padding: 2px;">Cost and types of other investigations/procedures (e.g. biopsy)</td> <td></td> </tr> <tr> <td style="padding: 2px;">Total cost tests/procedures no longer required</td> <td style="text-align: right;">£</td> </tr> </table>	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	£
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<p>36. REAL LIFE CASE STUDY n/a to additional provider applications In collaboration with the clinical lead, describe a <u>real</u> case example to illustrate how the test would improve patient experience.</p>										
<p>A 26 year old man who was the son of a <i>CYLD</i> mutation carrier wanted to start a family. He was aware of the significant impact the disease could carry and wanted to know if he carried the altered gene. As the genetic mutation was known in his family, he was tested and found not to carry a mutant copy of the gene. This allowed him to start a family without concern that he may have children that would be at risk if multiple skin tumours and disfiguring facial surgery.</p>										

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

The cost saving in this condition is difficult to quantify.

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 £

The cost saving in this sample is difficult to quantify

UKGTN Testing Criteria

Test name: Familial Cylindromatosis, Trichoepitheliomas and Spiradenoma

Approved name and symbol of disease/condition(s): Brooke-Spiegler Syndrome; BRSS Trichoepithelioma, Multiple Familial, 1 Cylindromatosis, Familial	OMIM number(s): 605041 601606 132700
Approved name and symbol of gene(s): cylindromatosis (turban tumor syndrome); CYLD	OMIM number(s): 605018

Patient name:	Date of birth:
Patient postcode:	NHS number:
Name of referrer:	Lab ID:
Title/Position:	

Referrals will only be accepted from one of the following:	
Referrer	Tick if this refers to you.
Consultant Clinical Geneticist	
Consultant Dermatologist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	Tick if this patient meets criteria
Multiple tumours – trichoepithelioma, cylindroma, spiradenoma OR	
Single tumour - trichoepithelioma, cylindroma, spiradenoma and a family history of a first degree relative with any of these tumours OR	
Asymptomatic family member at 50% risk and known mutation in family	

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.