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

Submitting laboratory: Manchester RGC

1. Disorder/condition – approved name (please provide UK spelling if different from US) and symbol as published on the OMIM database (alternative names will be listed on the UKGTN website).
If NGS panel test, please provide a name.

If this submission is for a panel test please complete appendix 1 listing all of the conditions included using approved OMIM name, symbol and OMIM number.

Schwannomatosis & Rhabdoid Tumour 2 Gene Panel

2. OMIM number for disorder/condition

If a panel test – see 1. Above. If a number of subpanels exist with different clinical entry points e.g. cancer panel test but different subpanels for different types of cancer (breast cancer, colon, phaeochromocytoma) , then please list the sub panels here:

OMIM#162091, OMIM#615670 & OMIM#609322

3a. Disorder/condition – please provide, in laymen's terms, a brief (2-5 sentences/no more than 50 words) description of how the disorder(s) affect individuals and prognosis.

Schwannomas are benign tumours of the nervous system. Schwannomatosis is an adult-onset tumour predisposition syndrome characterized by the development of multiple schwannomas in various areas of the body. The extent to which the disorder affects individuals depends on the location and number of schwannomas. Schwannomas on the arms and legs cause pain, whereas schwannomas of the spinal nerve root can cause limb weakness or loss of sensation.

Rhabdoid tumours are highly malignant tumours with a poor prognosis which tend to occur in children less than 2 years of age. Rhabdoid tumour predisposition syndrome is an autosomal dominant cancer syndrome predisposing to malignant rhabdoid tumors of the kidneys and elsewhere and to a variety of tumours of the central nervous system.

3b. Disorder/condition – if required please expand on the description of the disorder provided in answer to Q3a.

4. Disorder/condition – mode of inheritance
If this submission is for a panel test, please complete the mode of inheritance for each condition in the table in appendix 1.

Autosomal dominant for germline inactivating mutations – see Appendix 1.

5. Gene – approved name(s) and symbol as published on HGNC database (alternative names will be listed on the UKGTN website)
If this submission is for a panel test please complete appendix 1 listing all of the genes included using approved HGNC name, symbol, number and OMIM number. Please provide subpanel split (described in Q2 above) in appendix 1.

See Appendix 1.

6a. OMIM number(s) for gene(s) If a panel test – see 5. above
See Appendix 1.
6b. HGNC number(s) for gene(s) If a panel test – see 5. above
See Appendix 1.
7a. Gene – description(s) If this submission is for a panel test, please provide total number of genes and if there are subpanels, please also list the number genes per sub panel.
2 genes LZTR1 – 21 exons; SMARCB1 – 9 exons
7b. Number of amplicons to provide this test (molecular) or type of test (cytogenetic) (n/a for panel tests)
13
7c. GenU band that this test is assigned to for index case testing.
E
8. Mutational spectrum for which you test including details of known common mutations (n/a for panel tests) If this application is for a panel test to be used for different clinical phenotypes and/or various sub panel tests – please contact the team for advice before completing a Gene Dossier
Point mutations and small insertion and deletions for the whole coding sequence of both genes including immediate intron exon boundaries and the relevant 3' UTR for SMARCB1. Copy number analysis by MLPA for SMARCB1.
9a. Technical method(s) – please describe the test.
Enrichment by long PCR followed by use of Illumina Nextera XT for indexing and library preparation. Then next generation sequencing using Illumina MiSeq and bioinformatics analysis using a custom analysis pipeline.
9b. For panel tests, please specify the strategy for dealing with gaps in coverage.
Sanger sequencing will be performed to deal with gaps in coverage.
9c. Does the test include MLPA? **(For panel tests, please provide this information in appendix 1)**
Yes for SMARCB1.
9d. If NGS is used, does the lab adhere to the Association of Clinical Genetic Science Best Practice Guidelines for NGS?
Yes.

10. Is the assay to be provided by the lab or is it to be outsourced to another provider?
If to be outsourced, please provide the name of the laboratory and a copy of their ISO certificate or their CPA number.

By the laboratory.

11. Validation process
Please explain how this test has been validated for use in your laboratory, including calculations of the sensitivity and specificity for the types of mutations reported to cause the clinical phenotype. Note that the preferred threshold for validation and verification is ≥95% sensitivity (with 95% Confidence Intervals). Your internal validation documentation can be submitted as an appendix (and will be included in the published Gene Dossier available on the website). The validation information should include data on establishing minimum read depth and horizontal coverage for the regions of interest, reproducibility of the pipeline, accuracy of variant calling, filtering of common variants and artefacts.
If this submission is for a panel test, please provide a summary of evidence of instrument and pipeline validation and complete the tables below.

See attached document.

The assay technology being used is based on a long range PCR approach followed by Nextera XT library preparation and Illumina MiSeq v2 2x150bp sequencing. Data is analysed using a custom bioinformatics pipeline. This approach including the bioinformatics pipeline is in routine use in the laboratory and was validated initially for BRCA1/2 analysis and then verified on a range of other genes that have migrated from Sanger to NGS analysis. The overall sensitivity determined from the BRCA1/2 validation was ≥99.6% (95%CI) and indel mutations up to 40bp in size were tested for and routinely detected. Mutations and variants when identified are confirmed by Sanger sequencing. A small number of false positive calls are made by the pipeline however these are filtered by a combination of defined criteria and Sanger confirmation hence the specificity of the overall assay is extremely high.

Further details of the assay validation are included as an attachment.

For panel tests:

Sensitivity ≥89.3% (95% CI)*

Read depth minimum cut off: 100x

**derived solely from validation/verification data for SMARCB1/LZTR1 assay, see preamble for sensitivity derived from the full methodology validation conducted by our laboratory*

	Previously tested	**NGS test concordant results**	**NGS False negative**
Number of patient samples	**18**	**18**	**0**
Unique variants (total)	**23**	**23**	**0**
SNV	**20**	**20**	**0**
Indel (1bp to 6bp)	**3**	**3**	**0**
CNV	**N/A**	**N/A**	**N/A**

If a reference sample (eg HapMap/CEPH DNA) has been tested please complete this table too:

	Known variants	**NGS test concordant results**	**NGS False negative**
Reference sample details – Coriell cell line NA18533	**5**	**5**	**0**
Unique variants (total)	**5**	**5**	**0**
SNV	**5**	**5**	**0**
Indel (1bp to X bp)	**0**	**0**	**0**
CNV	**N/A**	**N/A**	**N/A**

Specificity ≥84.3% (95% CI)*

**derived solely from validation/verification data for SMARCB1/LZTR1 NGS assay, see preamble for further details of the full NGS methodology validation conducted by our laboratory*

	Variant confirmed by other method	NGS False positive
Number of patient samples with a variant detected by NGS	**18**	**0**
Unique variants (total)	**23**	**0**
SNV	**20**	**0**
Indel (1bp to X bp)	**3**	**0**
CNV	**N/A**	**N/A**

12a. Are you providing this test already?

Yes. The test has evolved from a Schwannomatosis/RTPS1 service based on SMARCB1 screening alone. We currently deliver this by Sanger sequencing and MLPA.

12b. If yes, how many reports have you produced?

Sanger Based Tests	NGS Based Tests
346	0

12c. Number of reports with a pathogenic (or likely pathogenic) mutation identified?

Sanger Based Tests	NGS Based Tests
52	0

12d. Please provide the time period in which these reports have been produced and whether in a research or a full clinical diagnostic setting.

Since Dec 2008 in a full clinical diagnostic setting.

13a. Is there specialised local clinical/research expertise for this disorder?

Yes

13b. If yes, please provide details

Prof Gareth Evans and Dr Susan Huson who are both Consultant Clinical Cancer Geneticists and acknowledged experts in the field of Neurofibromatosis and Schwannomatosis are based in the Manchester Centre for Genomic Medicine and provide clinical advice and support for the service.

Prof G Evans and Dr M Smith have a research interest in this condition.

14. If using this form as an Additional Provider application, please explain why you wish to provide this test as it is already available from another provider.

N/A

EPIDEMIOLOGY

15a. Estimated prevalence of conditions in the general UK population

Prevalence is total number of persons with the condition(s) in a defined population at a specific time.

e.g. CF prevalence approx. 12 per 100,000 with UK population of approx. 63 million the prevalence of affected individuals in the UK is 7560

Please identify the information on which this is based.

For panel tests, please provide estimates for the conditions grouped by phenotypes being tested.

Unknown.

15b. Estimated annual incidence of conditions in the general UK population

Incidence is total number of new cases in a year in a defined population. e.g. CF incidence 1/2650 live births in a UK population with 724,000 live births in a year = 273 new cases a year

Please identify the information on which this is based.

For panel tests, please provide for groups of conditions.

Only paper on epidemiology of Schwannomatosis from Finland suggests similar birth incidence to NF2. However, we estimate that it is around 1 in 100,000 similar to the actual figure from Finland.

16. Estimated gene frequency (Carrier frequency or allele frequency)

Please identify the information on which this is based.

n/a for panel tests.

No population testing. LZTR1 + SMARCB1 accounts for about 70% of familial Schwannomatosis and 25% of isolated sporadic (Smith et al Neurology 2014).

SMARCA4 mutations occur in the minority of rhabdoid tumours without SMARCB1 protein loss. Reports will suggest IHC staining of the original tumour for SMARCB1.

17. Estimated penetrance of the condition. Please identify the information on which this is based

n/a for panel tests

Based on segregation 80-90%.

18. Estimated prevalence of conditions in the population of people that will be tested.

n/a for panel tests.

LZTR1 + SMARCB1 accounts for about 70% of familial schwannomatosis and 25% of isolated sporadic (Smith et al Neurology 2014).

INTENDED USE (Please use the questions in Annex A to inform your answers)

19. Please tick either yes or no for each clinical purpose listed.

Panel Tests: a panel test would not be used for pre symptomatic testing, carrier testing and pre natal testing as the familial mutation would already be known in this case and the full panel would not be required.

Diagnosis	☒ **Yes**	☐ **No**
Treatment	☐ **Yes**	☒ **No**
Prognosis & management	☒ **Yes**	☐ **No**
Presymptomatic testing (n/a for Panel Tests)	☐ **Yes**	☐ **No**
Carrier testing for family members (n/a for Panel Tests)	☐ **Yes**	☐ **No**
Prenatal testing (n/a for Panel Tests)	☐ **Yes**	☐ **No**

TEST CHARACTERISTICS

20. Analytical sensitivity and specificity

-The *analytical sensitivity* of a test is the proportion of positive results correctly identified by the test (true positive/true positive + false negative). The *analytical specificity* of a test is the proportion of negative results correctly identified by the test (true negative/true negative + false positive).

This should be based on your own laboratory data for (a) the specific test being applied for or (b) the analytical sensitivity and specificity of the method/technique to be used in the case of a test yet to be set up. Please specify any types of mutations reported to cause the clinical phenotype that cannot be detected by the test.

Note that the preferred threshold is ≥95% sensitivity (with 95% Confidence Intervals).

The assay technology being used is based on a long range PCR approach followed by Nextera XT library preparation and Illumina MiSeq v2 2x150bp sequencing. Data is analysed using a custom bioinformatics pipeline. This approach including the bioinformatics pipeline is in routine use in the laboratory and was validated initially for BRCA1/2 analysis and then verified on a range of other genes that have migrated from Sanger to NGS analysis. The overall sensitivity determined from the BRCA1/2 validation was ≥99.6% (95%CI) and indel mutations up to 40bp in size were tested for and routinely detected. Mutations and variants when identified are confirmed by Sanger sequencing. A small number of false positive calls are made by the pipeline however these are filtered by a combination of defined criteria and Sanger confirmation hence the specificity of the overall assay is extremely high.

Large rearrangements of LZTR1 i.e. multi-exon deletions/duplications are not detected by the assay but will be included once an MLPA assay becomes available (this is in development by MRC-Holland)

For panel tests:

Sensitivity ≥89.3% (95% CI)*

Read depth minimum cut off: 100x

**derived solely from validation/verification data for SMARCB1/LZTR1 assay, see preamble for sensitivity derived from the full methodology validation conducted by our laboratory*

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If a reference sample (eg HapMap/CEPH DNA) has been tested please complete this table too:

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CNV	**N/A**	**N/A**	**N/A**

Specificity ≥84.3% (95% CI)*

**derived solely from validation/verification data for SMARCB1/LZTR1 assay, see preamble for information regarding the full methodology validation conducted by our laboratory*

	Variant confirmed by other method	NGS False positive
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CNV	**N/A**	**N/A**

21. 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 disorder is known to be absent. The denominator in this case is the number with the disorder (for sensitivity) or the number without condition (for specificity).

Please provide the best estimate. UKGTN will request actual data after one year service.

For a panel test, the expected percentage diagnostic yield for the test in the target population can be presented as an alternative to clinical sensitivity and specificity?

22. 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).

Not currently requested for panel tests

N/A

23. Testing pathway for tests where more than one gene is to be tested sequentially

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 will be added to the published Testing Criteria.

n/a for panel tests

N/A

CLINICAL UTILITY

24. How will the test change the management of the patient and/or alter clinical outcome? Please summarise in 2-3 sentences – no more than 50 words.

Schwannomatosis is not associated with reduced life expectancy but does cause substantial morbidity especially from pain. Testing negative in a family with a mutation will be extremely reassuring and mean no surveillance is necessary. Negative testing in the proband is reassuring with regard to transmission risks to offspring especially when combined with SMARCB1. LZTR1 also confers some risk of vestibular schwannoma. Bevacizumab is a VEGFa antibody that has shown efficacy in treating schwannomas in both NF2 and schwannomatosis. Currently around 60 NF2 patients are receiving treatment as of April 2015 through the highly specialised NF2 service in England.

Identification of two mutations in a Rhabdoid tumour (ie SMARCB1) but none in blood will make it unlikely that there is a germline mutation and this significantly reduces the risks to siblings. A small proportion of those without a germline mutation maybe mosaic.

25. Please provide full description on likely impact on management of patient and describe associated benefits for family members. If there are any cost savings AFTER the diagnosis, please detail them here.

It will allow presymptomatic testing and counselling and clarify risks of tumours in comparison with mosaic NF2. Allows targeting of MRI on spine and not brain

Savings from not having to MRI those that test presymptomatically negative, and reassurance to those shown not to be at risk

Identification of the mutation in the germline of a patient with rhabdoid tumour will allow exclusion testing to siblings and prenatal testing as parental mosaicism is relatively frequent.

26. If this test was not available, what would be the consequences for patients and family members? Please describe in not more than 50 of words.

If not able to exclude inheritance of the condition, management would have to be expectant with far greater costs from regular unnecessary MRI. In Schwannomatosis this will involve regular review with whole body MRI screening every 3-5 years for those at 50% risk. In those with an affected parent but no other family history there would have to still be some concern that they will have inherited a mutation. In ATRT it will also save unnecessary screening of infants.

27. 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.

MRI scans cannot exclude inheritance of a mutation. Whole body MRI can now pick up small schwannomas but these may not appear until aged 40 or later. Even after this age a negative scan will not exclude disease. In ATRT only a scan diagnosis can confirm inheritance again scanning even after infancy cannot exclude a mutation as non penetrance is described.

28. What unexpected findings could this test show? For example, lung cancer susceptibility when testing for congenital cataract because ERCC6 gene (primarily associated with lung cancer) is included in a panel test for congenital cataract.

None known

29. Please list any genes where the main phenotype associated with that gene is unrelated to the phenotype being tested by the panel.

N/A

30. If testing highlights a condition that is very different from that being tested for, please outline your strategy for dealing with this situation.

N/A

31. If a panel test, is this replacing an existing panel/multi gene test and/or other tests currently carried out by your lab e.g. Noonan Spectrum Disorders 12 Gene Panel replaced multigene Sanger test for KRAS, RAF1, PTPN11 and SOS1? If so, please provide details below.

Yes this test will replace the current Sanger screening service for SMARCB1 analysis.

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

None.

33. REAL LIFE CASE STUDY
Please provide a case study that illustrates the benefits of this test

A 45 year old presents with a history of severe pain from multiple schwannomas. She has two children, one her carer, who are at risk. Identification of an LZTR1 mutation in the proband allows predictive testing of her children. The children having tested negative, the grandchildren are no longer at risk of developing disease resulting in reduced anxiety and lower burden on the healthcare system.

A mother has had two children who died from ATRT but is unaffected herself. A mutation in SMARCB1 was identified in her blood allowing prenatal testing of the next pregnancy. A mutation negative result on the prenatal sample results in a huge reduction in parental anxiety and paediatric monitoring of the child.

UKGTN Testing Criteria

Test name: **Schwannomatosis & Rhabdoid Tumour 2 Gene Panel**	
Approved name and symbol of disorder/condition(s):	**OMIM number(s):**
Schwannomatosis 1; SWNTS1	*#162091*
Schwannomatosis 2; SWNTS2	*#615670*
Rhabdoid Tumour Predisposition Syndrome 1; RTPS1	*#609322*
Approved name and symbol of gene(s):	**OMIM number(s):**
SWI/SNF-Related, Matrix-associated, Actin-dependent Regulator of Chromatin, subfamily B, member 1; SMARCB1	**601607*
Leucine Zipper-like Transcriptional Regulator 1; LZTR1	**600574*

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	
Consultant Paediatric Oncologist (for Rhabdoid tumour cases)	
Consultant Neurologist (for Schwannomatosis)	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
For Rhabdoid tumour predisposition syndrome: Child with atypical teratoid/rhabdoid tumour (ATRT) or malignant rhabdoid tumour (MRT) showing loss of SMARCB1 on immunohistochemistry	
For Schwannomatosis: A family history of schwannomatosis Two or more schwannomas (no vestibular schwannoma or cutaneous plaques) AND negative for NF2 mutations in blood DNA	

Additional Information:
For panel tests:
At risk family members where familial mutation is known do not require a full panel test but should be offered analysis of the known mutation.

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.

IS IT A REASONABLE COST TO THE PUBLIC?

37. Based on experience what will be the national (UK wide) activity, per annum, for:

Index cases 40

Family members where mutation is known 25

38. If your laboratory does not have capacity to provide the full national need please suggest 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. If you are unable to answer this question please write "unknown".

N/a we can manage full UK test load

39. In order to establish the potential costs/savings that could be realised in the diagnostic care pathway, please list the tests/procedures that are no longer required to make a diagnosis if the index case has a definitive molecular genetic diagnosis from the test proposed in this gene dossier.

	Type of test	Cost (£)
Imaging procedures	MRI spine and Brain	1000 plus repeats every 5 years if negative
Laboratory pathology tests (other than molecular/cyto genetic test proposed in this Gene Dossier)	N/a	
Physiological tests (e.g. ECG)	N/a	
Other investigations/procedures (e.g. biopsy)	N/a	
Total cost of tests/procedures no longer required (please write n/a if the genetic test does not replace any other tests procedures in the diagnostic care pathway)		**£1000**

40. Based on the expected annual activity of index cases (Q37), please calculate the estimated annual savings/investments based on information provided in Q39.

Number of index cases expected annually	40
Cost to provide tests for index cases if the genetic test in this Gene Dossier was not available (see Q39)	£1000
Total annual costs per genetic test submitted for evaluation in this Gene Dossier	40,000
Total annual costs to provide genetic test	19,320
Additional savings for 100% positive rate for index cases	20,680 (this is annual cost, scanning cost is recurrent)
Percentage of index cases estimated to be negative	60%
Number of index cases estimated to be negative	24
Costs to provide additional tests for index cases testing negative	24 x £1000 = £24,000
Total investment for tests for index patient activity	£3320
Total costs for family members	Costs for family member test n number of family members expected to test in a year 25 x 138 = 3450
If there is a genetic test already available and some of the family testing is already being provided, please advise the cost of the family testing already available	Cost for family member testing already available 16 estimated number of tests for family members already provided (k) 16 x 138 = 2208
Total costs for family members minus any family member testing costs already provided	1242
Additional costs for all activity expected in a year	£3320 + £1242 = £4562

41. Please indicate the healthcare outcomes that apply to this test after diagnosis. It is recognised that all tests recommended by the UKGTN for NHS service improve clinical management and, if a familial mutation is found, allows for prenatal testing and therefore these are not included in the list below.

Healthcare outcomes	Does this apply to this test?
1. Genetic testing alerts significant clinical co-morbidities	Yes
2. Reduced mortality/saves lives	No
3. Avoids diagnostic invasive procedures/tests and associated in patient episodes	Yes
4. Confirms targeted therapy	Yes Avastin
5. Earlier diagnosis avoiding multi hospital appointments /procedures	Yes
6. Avoids irreversible harm	No
7. Enables access to educational and social support	No
8. At risk family members that test negative for a familial mutation can be discharged from follow up	Yes
9. At risk family members that test positive have appropriate follow up	Yes

Appendix 1

Genes in panel test and associated conditions.

Rows that are highlighted in yellow show where the gene is currently being fully analysed in the context of a single separate UKGTN test.

OMIM standard name of condition and symbol	Mode of inheritance	OMIM No	HGNC standard name and symbol of the gene	HGNC No	OMIM No	Evidence of association between gene(s) and condition	% of horizontal coverage of gene	MLPA	Comments
SCHWANNOMATOSIS 1; SWNTS1	AD	162091	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1; SMARCB1	11103	*601607		100% of coding region of gene (+/- 15base pairs) and 3'UTR to c.*100	Yes	
SCHWANNOMATOSIS 2; SWNTS2	AD	615670	Leucine-zipper-like transcription regulator 1; LZTR1	6742	*615670	Piotrowski et al., (2014) Germline loss-of-function mutations in LZTR1 predispose to an inherited disorder of multiple schwannomas. Nat Genet. 46(2):182-7. Paganini et al., (2014) Expanding the mutational spectrum of LZTR1 in schwannomatosis. Eur J Hum Genet. [Epub ahead of print] Smith et al., (2014) Mutations in LZTR1 add to the complex heterogeneity of schwannomatosis. Neurology. [Epub ahead of print]	100% of coding region of gene (+/- 15base pairs)	No	MLPA kit being created and will be incorporated once available

Rhabdoid Tumour Predisposition Syndrome 1; RTPS1	AD	*609322*	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1; SMARCB1	11103	*601607	Versteege, I., Sevenet, N., Lange, J., Rousseau-Merck, M.-F., Ambros, P., Handgretinger, R., Aurias, A., Delattre, O. Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer. Nature 394: 203-206, 1998. Swensen, J. J., Keyser, J., Coffin, C. M., Biegel, J. A., Viskochil, D. H., Williams, M. S. Familial occurrence of schwannomas and malignant rhabdoid tumour associated with a duplication in SMARCB1.	100% of coding region of gene (+/- 15base pairs) and 3'UTR to c.*100	Yes	