UAB MEDICAL GENOMICS LABORATORY

Schwannomatosis/Multiple Schwannoma Panel by Next-Gen Sequencing (SCH-NG)

Ordering Information

Acceptable specimen types:

- Blood (3-6ml EDTA; no time limitations associated with receipt)
- Saliva (OGR-575 DNA Genotek; kits are provided upon request)
- DNA (extracted from lymphocyte cells, a minimum of25µL at a concentration of 3µg, O.D. value at 260:280nm ≥1.8)
- A minimum of 2 anatomically distinct tumor samples is suggested, however, a single tumor can be provided.
    - Flash frozen tumor sent on dry ice*
    - Fresh tumor or affected tissue biopsy, immersed in sterile culture media (PBS/RPMI)*
    - Tumor block should have a surface area ≥ 5mm squared or the specimen contains at least 3-6 loose paraffin curls (no slides) that are 30-50 microns thick*

*Specimen should contain at least 70% pure tumor content and >80% nucleated cells

Turnaround time:

30 working days for blood, saliva, or DNA

40 working days for fresh/frozen tumor or tumor block

Price, CPT codes, and Z code:

$1,500 for blood, saliva, or DNA (USD – institutional/self-pay);

$2,500 for fresh/frozen tumor or tumor block (USD – institutional/self-pay);

CPT: 81406, 81405, and 81479 (x3)

720 Twentieth Street South, Suite 330 Phone: (205) 934-5562
Birmingham, Alabama 35294-0005 Fax: (205) 996-2929
www.uab.edu/medicine/genetics/medical-genomics-laboratory

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Z codes: ZB67Y

Candidates for this test:

Patients with multiple schwannomas with or without vestibular schwannomas. This testing approach was developed to diagnose mosaic *NF2-*, *LZTR1-*, and *SMARCB1*-related schwannomatosis, as well as classic *NF2-*, *LZTR1-*, and *SMARCB1*-related schwannomatosis

Specimen shipping and handling:

- Please find acceptable specimen type above.
- All submitted specimens must be sent at room temperature. DO NOT ship on ice.
- Specimens must be packaged to prevent breakage and absorbent material must be included in the package to absorb liquids in the event that breakage occurs. Also, the package must be shipped in double watertight containers (e.g. a specimen pouch + the shipping company's diagnostic envelope).
- To request a sample collection kit, please visit the website or email medgenomics@uabmc.edu to complete the specimen request form.
- Please contact the MGL (via email at medgenomics@uabmc.edu, or via phone at 205-934-5562) prior to sample shipment and provide us with the date of shipment and tracking number of the package so that we can better ensure receipt of the samples.

Required forms:

- Test Requisition Form
- Form for Customs (for international shipments)

Note: Detailed and accurate completion of this document is necessary for reporting purposes. The Medical Genomics Laboratory issues its clinical reports based on the demographic data provided by the referring institution on the lab requisition form. It is the responsibility of the referring institution to provide accurate information. If an amended

report is necessary due to inaccurate or illegible documentation, additional reports will be drafted at charge.

Requests for testing may not be accepted for the following reasons:

- No label (patients full name and date of collection) on the specimens
- No referring physician's or genetic counselor's names and addresses
- No billing information
- DNA samples must be extracted in a CLIA or equivalent certified lab

For more information, test requisition forms, or sample collection and mailing kits, please call: 205-934-5562.

Disorder Background

Schwannomas are nerve sheath tumors which are nearly always benign but can cause significant pain. Isolated schwannomas are common in the population, but the development of multiple non-intradermal schwannomas (in the absence of bilateral vestibular schwannomas, congenital cataracts or ependymomas, typically associated with constitutional NF2) as typically seen in schwannomatosis patients, is rare. The presence of multiple non-intradermal schwannomas, in the absence of a family history of *NF2*-related schwannomatosis, can be found in individuals with mosaic *NF2*-related schwannomatosis, or in individuals carrying germline variants in either *SMARCB1* or *LZTR1*.

People with *LZTR1*- and *SMARCB1*-related schwannomatosis do not typically develop bilateral vestibular schwannomas, ependymomas, meningiomas (typically associated with *NF2*-related schwannomatosis), nor neurofibromas or astrocytomas (associated with NF1). However, significant clinical overlap with *NF2*-related schwannomatosis exists: some *SMARCB1*-positive patients have developed meningiomas or a unilateral vestibular schwannoma; and some *LZTR1*-

positive patients have been reported with a unilateral/bilateral vestibular schwannoma. Whereas schwannomatosis presents with variable expressivity, penetrance for *NF2*-related schwannomatosis is close to 100%, whereas non-penetrance is well documented in *LZTR1*- and *SMARCB1*-related schwannomatosis, although the exact frequency is not known.

Test Description

The **Schwannomatosis/Multiple Schwannoma Panel by NGS** involves the simultaneous sequencing of 3 genes: *NF2, SMARCB1,* and *LZTR1*. The test uses an extensively customized and optimized set of Agilent HaloPlex capture probes, followed by sequencing of overlapping amplicons within the regions of interest using 300bp paired-end Illumina sequencing chemistry. Each coding exon plus ~50bp of flanking intronic sequence are simultaneously sequenced. 5' and 3' untranslated sequences are not included. **The average coverage is >1600x with 100% of the coding region at ≥350x.** This allows for **detection of very low-level mosaicism** by sequencing (as low as 3% of the alleles in the coding region with >95% confidence).

Variant and copy number calls are made using a unique bioinformatics pipeline detecting all types of variants including single nucleotide substitutions, indels, and frameshifts caused by deletion/ duplication up to 112bp. Deletion/duplication analysis for *NF2*, *SMARCB1*, and *LZTR1* is included in this test, as such variants are a part of the variant spectrum for these conditions.

Relevant family members of a proband with any (novel or previously identified) variant of unknown significance are offered free of charge targeted analysis as long as accurate phenotypic data are provided by a health care professional to enhance the interpretation. There is no limitation to the number of relatives that can be tested free of charge.

For patients presenting with phenotypes that may overlap with these disorders, genetic analysis of the associated tumors may be beneficial in determining a diagnosis.

Tumor-based analysis can be performed on fresh or frozen tumor via next-generation sequencing. If the tumor specimen has been formalin-fixed paraffin embedded (FFPE) tumor,

please review our Sanger sequencing.

REFERENCES available on website.

Other related testing options:

- Next-Gen Sequencing and Deletion/Duplication analysis of *NF2* only (NF2-NG)
- Rhabdoid Tumor Predisposition Syndrome by Next-Gen Sequencing (RT-NG)

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