Updates from the International NF-SWN Genes Variant Curation Expert Panel (VCEP) to Improve Genetic Testing of Neurofibromatosis and Schwannomatosis

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Introduction: Neurofibromatosis type 1 (NF1), *NF2*, *SMARCB1*, and *LZTR1*-related schwannomatosis (SWN), and Legius syndrome (LGSS) require a genetic diagnosis (1) to confirm clinical suspicion in patients with indeterminate phenotype, (2) to better understand a patient's prognosis and (3) for family planning. Variant interpretation and classification of the five genes causing these disorders (*NF1*, *NF2*, *SMARCB1*, *LZTR1*, and *SPRED1*) is challenging due to the broad mutational spectrum, the paucity of clear mutational "hotspots", and the high proportion of non-coding and splicing variants. In addition, many of the patients do not have a family history due to high *de novo* and mosaicism rate and/or variable penetrance and expressivity and do not meet diagnostic criteria in the early stages of these disorders. These patients would benefit from an accurate genetic test for clinical use and follow-up.

Methods: Thirty-seven individuals from North and South America, Australia, and Europe with expertise in NF1, LGSS, and SWN (or other related hereditary tumor predisposition pathologies) or from high-volume diagnostic laboratories (academic and commercial) volunteered to develop ACMG/AMP variant interpretation rules specific for NF-SWN genes as members of a Variant Curation Expert Panel (VCEP) in the framework of the NIH-funded ClinGen Hereditary Cancer Clinical Domain Working Group. This panel of experts includes clinical and molecular geneticists, variant scientists, genetic counselors, epidemiologists, neurosurgeons, and others who regularly participate in the diagnosis and/or clinical management of this group of disorders.

Results: The NF-SWN Genes VCEP is comprised of five sub-VCEPs that will address causative genes associated with NF1 (*NF1*), LGSS (*SPRED1*), and SWN (*NF2*, *SMARCB1*, and *LZTR1*). For each disorder, a sub-VCEP has been organized into three working groups (functional, phenotypic, and computational) to review and modify, if required, the 26 general ACMG/AMP rules to establish specific criteria for each gene. Presently, the NF-SWN Genes VCEP has successfully developed the first version of *NF1* and *SPRED1* ACMG/AMP guidelines and has concluded the pilot study of *NF1* rules. A pilot study of *SPRED1* rules has begun recently. Furthermore, the establishment of SWN rules is underway, in conjunction with the analysis of *NF2*, *SMARCB1*, and *LZTR1* gene codes.

Conclusions: The NF-SWN Genes VCEP has been established with the objective of refining specific ACMG/AMP rules for use in curating NF-SWN gene variants. The primary aim of this initiative is to develop a compendium of NF-SWN gene-specific ACMG/AMP evidence rules. The eventual goal of this endeavor is to ensure more accurate variant interpretations for clinical use in the context of NF and SWN patients.