## RE: Cowden Syndrome and PTEN Hamartoma Tumor Syndrome: Systematic Review and Revised Diagnostic Criteria

We read the article by Pilarski et al. (1) and the accompanying editorial by Lachlan (2) with interest but disappointment. Pilarski et al. have proposed for consideration some revisions to the clinical criteria for diagnosis of PTEN hamartoma tumor syndrome (PHTS). However, these proposed revisions are based on a systematic review of published literature rather than detailed analysis of existing clinical datasets and have not been evaluated for validity in terms of calibration or concordance. This is unacceptable by modern standards of diagnostic criteria development. The authors report for only a limited number of individuals (n = 48) from a single institution that their proposed revisions yield a high sensitivity, without any determination of specificity. In the review, the authors have unaccountably failed to acknowledge the Cleveland Clinic (CC) score developed through the largest multicenter study of PHTS executed across North America, Europe, and Asia, involving 3026 probands and 290 individuals with confirmed germline *PTEN* mutations (3). This score involves an individualized risk assessment for germline *PTEN* mutations in adults and is available through an online risk calculator (http://www.lerner.ccf.org/gmi/ccscore/), which is in routine use in expert cancer genetics centers worldwide (4).The CC score has demonstrated superior performance in patient diagnosis in comparison with the National Comprehensive Cancer Network (NCCN) clinical criteria for PHTS, which one of us (C. Eng) participated in drafting (5), and the CC score has been externally validated in a prospective cohort centralized at The Ohio State University (3). Further, we read the accompanying editorial by Lachlan (2) with some puzzlement: we cannot agree that our risk assessment for determining individualized probability of germline *PTEN* mutation has a different aim compared with an effort to define "diagnostic criteria" of Cowden syndrome. The CC score can be and has been benchmarked against conventional diagnostic criteria, with markedly better predictive ability. Finally, Lachlan notes that a 5-year-old girl with autistic spectrum disorder, macrocephaly greater than the 97th percentile, motor delay, lipoma, and vascular abnormalities would not have qualified under current or previous NCCN criteria for testing. We wish to point out that that this patient would have clearly qualified under our specialized pediatric criteria (3) developed on the same global multicenter study where the adult CC score was established for adults. This pediatric criterion for PHTS is essentially macrocephaly (>95th percentile) and at least one of the following features: autism, relevant dermatologic features, vascular features such as arteriovenous malformations, and gastrointestinal polyps. Although research on rare diseases is inevitably fraught by a degree of ascertainment bias, efforts to minimize this bias must rely on appropriately selected, large, prospective, multicenter studies, particularly for the development of diagnostic criteria crucial for service to patients. We trust that such evidence based on global experience, painstaking data collection, and outcomes assessment will be considered at the next revision of the NCCN clinical criteria for PHTS.

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### References

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