We read with interest the recent article by Tan and colleagues (1), summarizing their experience in germline PTEN genetic testing. There is certainly a need for information about lifetime cancer risks for individuals with deleterious PTEN mutations and the authors’ data set will be helpful in defining this phenotype. However, the very high lifetime cancer risks they reported are not consistent with our clinical impressions of the PTEN patients and families we work with, and we believe that the data presented are subject to a strong ascertainment bias that would significantly overestimate cancer risk, therefore calling into question the reported lifetime cancer risks as well as the cancer screening recommendations derived therein. Specifically, 80% (295 of 368) of the PTEN-positive patients included in this report were recruited for the study on the basis of clinical criteria that included personal history of breast, endometrial, thyroid, and renal cancer (2). Because participants were selected on the basis of having cancer, they of course have a higher incidence of cancer than the chosen comparison group (general population SEER data). This does not prove, however, to what extent the observed cancers are actually due to the presence of the PTEN mutation. In addition, there is referral bias likely in favor of having personal and family history of cancer, given that study participants were recruited from cancer genetics clinics. Simply noting the possibility of ascertainment bias without adjusting data analysis to account for it, as the authors have done, is not sufficient. Multiple strategies for overcoming ascertainment bias in assessing lifetime cancer risk for hereditary cancer predisposition syndromes can be used (3, 4). As a preliminary step, the authors could separately report what cancers have developed over how many years of follow-up in the 73 study participants who were identified through predictive genetic testing after a family member enrolled in the study and therefore would not be subject to the same ascertainment bias as the probands. In addition, the authors report both truncating and nontruncating mutations (including promoter mutations) as deleterious. Because nontruncating and promoter mutations do not always disrupt gene function, the authors should report the data supporting the classification of nontruncating and promoter mutations as deleterious as per generally accepted standards (5). For these reasons, we believe that it is premature to recommend changes in clinical practice based on these data. We eagerly await the publication of additional data further elucidating the PTEN-positive phenotype.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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References
Lifetime Cancer Risks of \textit{PTEN} Mutation Carriers — Letter

Molly S. Daniels, Thereasa Rich, Scott Weissman, et al.