One step forward, two steps backward

To the Editor:

We wish to express our concerns about the policy statement of the American College of Medical Genetics and Genomics (ACMG) regarding secondary/incidental findings (SF) and population screening as it applies to cancer susceptibility genes.¹

In the first version of its recommendations, the ACMG stated that “reporting some incidental findings [of the ACMG 56] would likely have medical benefit for the patients and families of patients undergoing clinical sequencing.”² In a thoughtful final section of the second version (ACMG 59), the SF Working Group acknowledged the challenges and potential impact of reporting actionable SFs in diverse contexts, including healthy adults and the added complexity of communicating the less definitively interpreted findings.³ However, the recent clarification by the ACMG board is more restrictive than either of the previous full statements, focusing on the fact that the ACMG 59 has not been validated for general population screening, and emphasizing the fact that penetrance may be uncertain and interventions unproven in asymptomatic groups undergoing genetic analysis.

The ACMG is certainly right to anticipate the complexities that will accompany the release of the data from enormous population-based cohort projects, including All of Us (genotyping and whole genome sequencing (WGS) for one million participants) and the Electronic Medical Records and Genomics (eMERGE) Network. In eMERGE III, for instance, thousands of healthy participants have consented to undergo a sequencing panel of 110 actionable genes that includes the ACMG 59 list.⁴ One thoughtful model for coping with these challenges has been developed for the 100,000 Genomes Project in the UK, where a Genomic Clinical Interpretation Partnership is offering return of SF results (referred to as “additional” findings) from WGS, including pathogenic variants in some cancer predisposition genes.⁵

These concerns are understandable for many of the ACMG 59 genes, but difficult to apply fully for cancer susceptibility genes, which comprise 25 of the 59 genes, and for which cancer is often the sole phenotype. Established genotype–phenotype correlations have been documented and quantified for some prevalent founder variants within ethnicities and populations, such as the Ashkenazi *BRCA1/2* variants and the Icelandic variants in *MSH6* and *PMS2* genes.⁶ Many of these variants have been evaluated in large studies, much larger than typical studies of single-gene variants in extremely rare genetic syndromes. Further, the National Comprehensive Cancer Network and

other guidelines endorse germline testing in several cancer patient cohorts (e.g., all ovarian, pancreatic, castrate-resistant prostate, and metastatic breast cancer patients for therapeutic options), and the analysis of tumor and circulating cell-free DNA to enable identification of potential somatic therapeutic targets will increasingly include germline data, further expanding the reach of hereditary cancer risk assessment.⁷

In addition, it has been estimated that fewer than 10% of individuals with prevalent *BRCA1/2* and Lynch syndrome variants have been identified, while compelling cost-effectiveness studies of general and targeted population screening for breast/ovarian and Lynch-related mutation carriers show clear benefit to identification of unaffected carriers.^{8,9} We are not suggesting that all cancer susceptibility genes should be exempted. An example of a particularly challenging gene that has not been included in the ACMG list so far is *CDH1*, a highly penetrant gene within classic families, for which prophylactic gastrectomy and intensive breast surveillance are recommended in hopes of reducing mortality from highly lethal malignancies, in the absence, as yet, of definitive data on mortality reduction.¹⁰ Therefore, generalizing the risk reduction strategies to individuals for whom *CDH1* variants are identified as SF remains controversial.

Considering that policy statements, guidelines, and recommendations already exist and are constantly being revised, we are concerned that the new ACMG policy statement¹ is too restrictive for cancer susceptibility genes, and that the ACMG board should consider returning to the original statement of the ACMG 59 for this subset of actionable genes. We believe that acknowledging SF reporting through adult population screening for some prevalent highly penetrant cancer susceptibility genes is an important approach toward opportunistic cancer interception.

DISCLOSURE

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