ACMG response to Nussbaum et al. letter on ACMG policy statement: the use of secondary findings recommendations for general population screening: a policy statement of the ACMG

To the Editor:

The American College of Medical Genetics and Genomics (ACMG) appreciates the ongoing debate about genomic screening in asymptomatic individuals and the opportunity to respond to the letter from Nussbaum et al.¹ that comments on a clarification statement² related to our secondary findings recommendations³. We have been among the most progressive professional organizations in developing guidance on the integration of genomic sequencing into health care.^{3–5} This includes screening for genetic conditions in the prenatal, neonatal, pediatric, and adult settings. Our initial evaluation of secondary findings was an attempt to find a controlled environment in which genomic screening could develop. The secondary findings lists we published in 2013 and 2017 are appropriately constrained and offer an opportunity to provide real world data aggregation by those offering genome sequencing for medical indications.

We consider standardization of result reporting from genomic sequencing tests to be important to the public at large and our members. The ACMG Secondary Findings Maintenance Working Group (SFWG) uses a standardized methodology to assess the evidence for inclusion of a gene on the list, which is intentionally conservative. This effort is not unlike what was done when we proposed the initial list of variants appropriate for carrier screening in the *CFTR* gene for cystic fibrosis,⁶ which were later revised in a systematic fashion,⁷ or for our initial recommendations of a uniform panel for newborn screening.⁸ ACMG recognizes that there exists “...an appropriate balance between forces of ‘premature translation’ (i.e., the use of nonvalidated or potentially harmful genomic information in practice) versus ‘lost in translation’ (i.e., the endless study and evaluation of new technology with limited access across the population).”⁹ It is in this spirit that the ACMG SFWG continues to reassess their recommendations. Furthermore, the ACMG SFWG plans to accept nominations by “...professional specialty organizations, such as professional groups of genetic counselors, primary care clinicians, and other clinical specialists who may order or return results from GS [*sic*] and thereby encounter

SFs [*sic*] in their practice.”⁴ This approach mirrors the successful iterative processes employed with *CFTR* variants and newborn screening.

ACMG distinguishes between opportunistic screening, the reporting of secondary findings in individuals or any member of a trio who are having genomic sequencing done for clinical indications, as compared with screening asymptomatic individuals in the general population. As we said in our original statement “...the issues associated with genomic sequencing in healthy individuals of any age will become increasingly salient as costs decline and informatics interpretation algorithms improve, but the value of population screening for prevention and health promotion raises complex questions of potential benefits as well as downstream risks and costs that we need considerably more data to resolve.”³ While we are aware of current research studying the application of genomic screening to a population,¹⁰ we have not seen a comprehensive clinical utility assessment of genomic screening since our secondary findings recommendations were published.

In addition to analytical costs, there are costs associated with clinical follow-up after return of positive screening results. In the context of ACMG’s recommendation that variants for 59 genes be reported as secondary findings, we start with a smaller population of individuals and thus limit the number of individuals who are referred for follow-up. Among this group, reports suggest that 1–4% of those tested will have a medically actionable result.¹⁰ When used as a primary screening test, the number of people who are screened are significantly higher, as are the costs of clinical follow-up. We remain concerned that alleles with low penetrance will be identified frequently, compounding the costs of follow-up when screening asymptomatic patients.

A calculated, systematic approach to reporting secondary findings offers an opportunity to collect the data needed to inform important questions related to the age of onset/penetrance of the genetic risks and the range of severity associated with these risk factors. Knowledge of these variables is needed to inform the clinical validity and utility of genomic risk data. To date, there has been limited data sharing, so we are forced to aggregate data from small published, but often underpowered, studies. As explicitly stated in our secondary findings paper, the ACMG strongly supports research to develop the necessary evidence to allow critical evaluation of genomic screening at the population level.⁴

ACMG acknowledges there are several targets on the secondary findings list for which organized population-level pilot studies may be appropriate, such as the Centers for Disease Control and Prevention (CDC) tier 1 genes, and that several studies in the United States and elsewhere are

beginning to generate outcomes that will inform assessment of clinical utility and value. We also recognize the danger in moving forward with population-based screening in the absence of robust evidence.

We must ensure that (1) patients will not be harmed and (2) health-care costs will be balanced by increased quality of life. Short-term gains by industries promoting population-based exome sequencing without the rigor of peer reviewed publications and the opportunity for scrutiny and public debate have the potential to jeopardize the introduction of genetic technologies to improve care and quality of life at an affordable cost to the health-care system.

DISCLOSURE

The Board of the ACMG declares no conflicts of interest.

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