mutations they may carry that predict serious and medically actionable disease. For example, only 43% of 2,646 female first-degree relatives of patients with known *BRCA1/2* mutations in one study chose to be tested.[2]

In a qualitative study,[3] we explored patient, public, and professional views of disclosing genomic incidental findings. Patients and public groups emphasized patient choice while acknowledging difficulties around decision making. They emphasized having "the power" to choose disclosure or not, and that patients no longer accept medical paternalism. They also recognized practical difficulties of uncertain data interpretation and the difficulty of effective communication of extensive data to patients. However, our study participants emphasized that such challenges do not pose insurmountable barriers to patient choice. They suggested information be communicated to patients in novel and user-friendly computer-based formats that emphasize actively engaged and responsible patients and facilitate patient choice.

Another key concern prompted by the ACMG recommendations is the notion of coercive consent to testing and disclosure for vulnerable patients desperate to find the cause of a serious disorder. Although the recommendations claim that people can opt out, this is unlikely to be presented as a freely available choice in most instances. Some patients who prefer nondisclosure may decline whole-genome sequencing even though by doing so they lose the opportunity to end their diagnostic odyssey.

Rather than establish disclosure of a list of secondary genomic results regardless of patient preferences as a standard of care, it is important to consider patient perspectives and to understand what disclosure might mean in an individual's life context beyond the clinic. At every stage from "bench to bedside," the ACMG recommendations neglect patient viewpoints, and in doing so fail to provide patient-centered care, which is recognized as good practice in the rest of medicine. The recommendations, therefore, demonstrate an unfortunate kind of genetic exceptionalism.

We need to ask, "what are the barriers to informed choice?" We need more evidence and to draw fully on the evidence that we already have. Consensus among experts alone is not sufficient; recommendations that consider the patients' perspective will be more ethical and ultimately more effective. The paradox is that these recommendations at the cutting edge of medical practice are grounded in the past. By contrast, we call for the patient voice to be part of the decision-making process and for studies of patient concerns and perspectives to be incorporated into the evidence base for clinical genomics practice. We believe that these recommendations should be withdrawn and revised, taking into account existing research on patient concerns about genomic incidental findings as well as the results of direct consultations with genetic disease patients and their families. Further studies of patient perspectives and decision making in this context should also be encouraged.

DISCLOSURE

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Anne Townsend, PhD[1], Shelin Adam, MSc[1], Patricia H. Birch, MSc, RN[1] and Jan M. Friedman, MD, PhD[1]

[1]Friedman Lab, Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada. Correspondence: Anne Townsend (atownsen@exchange.ubc.ca)

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Response to Townsend et al.

To the Editor: I appreciate Townsend et al.'s thoughtful response ("Paternalism and the ACMG Recommendations on Genomic Incidental Findings: Patients Seen But Not Heard"[1]) to the "ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing."[2] The crux of their objection to the recommendations is that the input of consumers (or patients) was not sought as part of the process and that the recommendation that laboratories return results of specific incidental findings violates patient autonomy.

I am concerned that much of the discussion about the recommendations has been couched in terms such as "paternalism," "patient autonomy," "genetic exceptionalism," etc. I worry that these words tend to polarize arguments, making things seem more black and white than I think they are.

The key point that influenced the thinking of the working group, speaking from my own perspective as a member of the working group, is that the laboratory that interprets the sequencing and generates the report is not in a position to judge whether the person whose genome is sequenced should or should not be privy to results that could have life or death implications. We believe that this is the job of the clinician who has ordered the sequencing, who can take into account the perspectives and needs of his or her individual patient.

The analogy of reporting incidental findings from radiological studies is frequently cited in the context of the American College of Medical Genetics and Genomics recommendations.[2] It is an imperfect analogy; incidental findings sometimes jump out at the radiologist and may be difficult to consciously ignore. I have not heard arguments, however, that reporting such incidental findings in radiology violates patient autonomy and suspect that consenting all patients in advance who are about to have X-rays or other radiological studies would be viewed as impractical. Townsend et al.[1] make the point that incidental

radiological findings indicate disease that is currently present, whereas incidental genomic findings indicate disease that may some day be present. In fact, some of the radiological incidental findings do not diagnose disease; some are false positives that could lead to unnecessary invasive procedures. The time to discuss such incidental findings in radiology is when the clinician receives the radiology report, and is able to interpret the report in light of the patient's clinical status, personality, and life experience. I posit that the same is true for genomic incidental findings, recognizing that the American College of Medical Genetics and Genomics recommendations apply to a very narrow list of highly penetrant, well-annotated, and medically actionable findings.

Townsend et al.[1] also raised the point that the working group did not seek input from consumers (patients). This possibility was considered, but it was difficult to know who actually speaks for the general public on this issue. We ultimately decided to begin the discussion with input from scientific and medical experts, realizing that the recommendations would serve as a reference point for many perspectives. Townsend et al.[1] suggest that the recommendations be withdrawn and revised. I do not believe that they should be withdrawn, but as we stated in the report, I anticipate that they will be refined and revised in response to additional input and evidence. I especially agree with them that further research on patient perspectives and decision making should be encouraged. The working group felt, however, that genome sequencing is here with us now and that some statement was needed to provide a guideline to laboratories and clinicians actively struggling with this question. I hope that the recommendations will come to be seen in that light.

DISCLOSURE

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Bruce Korf, MD, PhD[1]

[1]Department of Genetics, University of Alabama at Birmingham, Birmingham, Alabama, USA. Correspondence: Bruce Korf (bkorf@uab.edu)

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Runs of homozygosity and parental relatedness

To the Editor: Several reports have drawn attention to the possibility that incidental evidence of parental relatedness can be uncovered in an individual who undergoes genomic testing for other purposes, and a recent article, "American College of Medical Genetics and Genomics: Standards and Guidelines for Documenting Suspected Consanguinity as an Incidental Finding of Genomic Testing,"[1] provides guidelines to clinical laboratory professionals for cases in which this scenario occurs. We wish to discuss new findings on runs of homozygosity (ROH) that could improve upon these recommended guidelines, thereby reducing the occurrence of false-positive and false-negative suggestions of parental relatedness on the basis of genomic testing.

Rehder et al.[1] recommended that the proportion of an individual genome located in homozygous segments whose lengths exceed a fixed threshold of 2–5 Mb can be compared with textbook autozygosity levels to suggest the level of relationship for the sampled individual. As recognized by Rehder et al.[1] and noted in studies of ROH features,[2,3] production of ROH is affected by forces acting on multiple time scales, including not only recent parental relatedness but also parental relatedness within a population at a level generally too distant for the parents to know of the relationship ("background relatedness"), and chance pairing of ancient haplotypes that have been magnified in frequency by founder events and subsequent population expansions. Recent parental relatedness, background relatedness, and founder events contribute primarily to ROH with long, intermediate, and short sizes, respectively, and in this context, the choice by Rehder et al.[1] to only consider ROH longer than a fixed threshold is an effort to identify only those ROH arising from recent parental relatedness. In relation to other studies that focused on a 1.5-Mb threshold,[2] the 2- to 5-Mb threshold level suggested by Rehder et al.[1] is comparable but more stringent.

The approach of applying a fixed threshold uniformly to all individuals can be improved in at least three ways. First, we have found that because of differences in the contribution of the various population-genetic processes to ROH patterns, the proportion of the genome consisting of homozygous segments differs across populations.[3] As a result, the demarcation of homozygous segments that are sufficiently long that they probably arose from recent parental relatedness lies at different sizes in different groups. For example, Native Americans, at the far extreme of the ancient out-of-Africa migration, have elevated homozygosity owing to ancient founder effects, and therefore their threshold length for attributing homozygous segments to recent parental relatedness is higher than that of Africans, who carry fewer long ancient homozygous regions. In small or isolated populations, the threshold can be higher than that in larger populations because limited mate choice can lead to high baseline levels of homozygosity even in the absence of consanguinity.

Second, we have developed a method that seeks to explicitly account for the different processes giving rise to ROH, separating ROH into three categories that largely correspond to different underlying processes—short "class A" ROH due to pairing of ancient haplotypes, intermediate "class B" ROH due to background relatedness in a given population, and long "class C" ROH due to recent parental relatedness.[3] In place of the recommendation of Rehder et al.[1] to compute F_{ROH}—the proportion