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COMMENTARY

Reevaluating the “right not to know” in genomics research

 Nina B. Gold^{1,2}  and Robert C. Green^{3,4,5,6,*} 

¹Division of Medical Genetics and Metabolism, Department of Pediatrics, Massachusetts General Hospital, Boston, MA; ²Department of Pediatrics, Harvard Medical School, Boston, MA; ³Division of Genetics, Department of Medicine, Brigham and Women's Hospital, Boston, MA; ⁴Ariadne Labs, Boston, MA; ⁵The Broad Institute of MIT and Harvard, Boston, MA; ⁶Department of Medicine, Harvard Medical School, Boston, MA

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In clinical exome or genome sequencing, the American College of Medical Genetics and Genomics (ACMG) has recommended that a minimum set of secondary findings for actionable conditions should always be offered to patients.¹⁻³ In the research domain, millions of individuals have been sequenced, but the return of actionable genomic results is rarely offered. In most research projects that do offer the return of genomic information, participants are asked at the outset whether they wish to be contacted with genomic results of medical importance in a consent process that often stresses potential harms, such as privacy threats or psychological distress, over potential benefits. If participants answer “no,” they are rarely asked again or offered the opportunity to change their response. Participants who decline the return of genomic information about themselves in research are said to be asserting their autonomy around the “right not to know.” The recent report by Schupmann et al⁴ challenges

this paradigm by showing that participants’ decisions about receiving unanticipated genomic information in research may change when they are given more information and an opportunity to reconsider. These findings prompt us to ask if we can expand autonomy by offering participants opportunities to change their choices, given new experiences in their lives or advances in medical science. Furthermore, should we more fundamentally reappraise the “right not to know” in research by routinely alerting participants to a specific finding within their own DNA and only then allowing them to decide how to proceed?

Although there is no accepted standard for the variants or genes to be returned in genomic research studies, many investigators return pathogenic and likely pathogenic variants in the genes on the ACMG list of secondary findings described earlier.¹⁻³ Even within this limited list, the type of disorder, penetrance and expressivity, and available treatments and surveillance protocols can vary widely. Some research participants who decline genetic information may not fully understand how such information might impact their lives. A man with syncopal episodes might not appreciate that a variant associated with arrhythmogenic right ventricular cardiomyopathy could provide an explanation for his symptoms and a course of action to address them. A woman with a family history of breast cancer might not recognize the scope of surveillance protocols available to *BRCA1*-positive individuals, wrongly assuming that her only option in the case of a positive finding would be

*Correspondence and requests for materials should be addressed to Robert C. Green, Department of Medicine, Brigham and Women's Hospital, 41 Avenue Louis Pasteur, Suite 301, Boston, MA 02115. E-mail address: rcgreen@bwh.harvard.edu

mastectomy. In these cases, prioritizing the right not to know with a single global question about returning genomic findings could preclude the disclosure of life-saving information. We rarely ask what happens to people who could have learned about medically actionable genomic information but declined results.

The report by Schupmann et al⁴ begins to address this question. The authors contacted more than 150 participants in a genomic research study who initially declined genetic results (“refusers”) and a cohort of individuals who had accepted them (acceptors). The researchers then provided participants with an educational intervention and asked if they would reconsider their original decision about receiving genetic findings. Importantly, roughly half of participants who had originally declined the return of results changed their decision (“reversible refusers”). Three-quarters of the reversible refusers believed that they had initially chosen to receive genetic results. The proportion of “persistent refusers,” those who were steadfast in their decision not to learn secondary genetic findings, was found to be less than 1% of the initial study population. The finding that a high percentage of refusers reconsidered their decision (and incorrectly recalled their initial choice) requires us to rethink how we ask about the return of genetic information in research. Should we take no for an answer, or at least for a permanent answer, when research participants initially decline actionable genetic results?

In considering this issue, we address 3 separate but interrelated questions.

Should Actionable Genetic Results Routinely Be Offered for Return in Genomic Research Studies?

The ACMG secondary findings recommendations have reified the importance of reporting actionable findings for patients who undergo clinical sequencing, and the opt-out process has revealed that most patients agree to receive them. We propose that returning actionable results to persons who have already had sequencing fulfills the ethical concept of “easy rescue,” an expression of beneficence that requires modest means or effort and is a concept that should now be extended to the research domain.⁵ Yet, among the millions of individuals throughout the world who have been sequenced in research studies, only a fraction have been offered genomic information. The reasons include logistical, regulatory, and payment hurdles.⁶ Nonetheless, the Global Alliance for Genomic Health recently approved a new policy linking the return of genomic results in research to the standards for clinical care in each country, including the return of secondary findings in clinical sequencing.⁷ For the United States, this would mean offering pathogenic and likely pathogenic variants in genes on the ACMG secondary findings list as a default option for every genomics research

project. We suggest that in the United States, it is no longer appropriate for research studies to conduct genomic research without offering participants actionable genetic results.

Should Research Participants Be Offered Genomic Information More Than Once?

Research studies that analyze genomic data may do so years or even decades after the participant is enrolled and has consented. Moreover, the value of a given piece of genomic information and the life experience of a research participant change over time. The data from Schupmann et al⁴ illuminate how dramatically participant opinions on genetic information can change over time. The National Institutes of Health–funded All of Us Research Program asks participants to opt into receiving risk variants in the initial consent process, and then the protocol attempts to provide an easy way to revisit their choices. Reevaluation of consent depends on continued contact and two-way engagement with participants, which can be challenging to maintain. Where feasible, we advise offering research participants a regular opportunity to change their minds about receiving actionable genomic information.

Can Autonomy Be Enriched by an Incremental Disclosure and Choice Process?

In most clinical research studies, it is expected that an abnormal, actionable finding on physical examination, laboratory testing, or imaging is simply communicated to the research participant. The participant is not usually queried about whether they wish to receive this information, although they can opt out of learning it by refusing to answer calls from the investigative team, or having heard the information, they can refuse to pursue further medical evaluation. The ACMG recommendations on secondary findings now provide a well-established recommendation to search for and offer to return actionable genomic findings in the clinical arena, which clinical patients can decline. But should we go even further in the research domain and avoid the simplistic choice of an opt-out? Perhaps the default in genomics research for those carrying actionable variants should be an initial notification, realizing that the research participant always has the right to decline further communication or the right not to act on unanticipated information. Indeed, if the participant is not alerted that they are carrying a risk factor for a specific actionable condition, how can they evaluate what their subsequent options might be?

The “right not to know” has legal, philosophical, and ethical foundations that have been thoughtfully reviewed in an analysis by Benjamin Berkman,⁸ the senior author of the Schupmann et al paper.⁴ Among the ideas in that analysis is

the notion that, although complete autonomy may be unachievable, autonomy can be maximized only when the information necessary to make a decision is present. Berkman also argues that the constitutionally protected right to refuse medical treatment is grounded in protecting bodily integrity and cannot be easily analogized to the return of genomic results, in which only psychological integrity is involved. Thus, we suggest that the debate over the “right not to know” should move toward a broader view of autonomy that more fully considers beneficence while still preserving the choices of research participants to act or not to act on information. Consent processes in research can be written to simply state that a participant will be contacted with medically important information, including actionable genomic findings. Individuals who strongly object to the psychological intrusion of genomic information, perhaps representing persistent refusers, could choose not to enroll in such research studies. For participants who consent to participate, personalized information about that particular gene and condition could be offered at the time of recontact. The report by Schupmann et al⁴ empirically strengthens this argument by showing that the initial rejection of genomic information is not particularly stable and may change over time or when more information is provided.

In our own protocol for genetic return of results within the Mass General Brigham Biobank, we have applied a novel “incremental disclosure and choice” process, wherein participants were initially consented for the Biobank without the ability to decline recontact and initial disclosure.⁶ When their DNA was analyzed, pathogenic and likely pathogenic variants in the ACMG version 2 list were sought, and any participant carrying such a variant who could be reached was alerted in general terms (“We found a DNA change related to increased risk of cancer”). Participants were then given the choice to accept additional information and counseling and ultimately confirm and learn the precise variant they were carrying. Although every available participant was alerted by phone or mail that they carried a medically important genomic finding, 37.5% of those who were reached elected not to pursue confirmation, thereby exercising their autonomy to avoid learning more about their genomic results. As previously emphasized by others,⁹ it could be argued that when it comes to unanticipated findings, autonomy is protected and even enriched by delivering disease-specific information at a time in which the participant can decide whether or not to act on it.

The ACMG secondary findings recommendations allow patients to opt out of receiving secondary findings. Insisting on returning secondary findings for diagnostic clinical sequencing could deter some patients from accepting the testing and, in that deterrence, harm the patient. The same argument does not apply in the research domain. There is no countervailing clinical evaluation that might be denied to participants who decline genomic information. Thus, we suggest that in future genomic research studies, consent for

return of results be reconfigured such that participants understand that they will be alerted if they are carrying an actionable finding and can then accept or decline more specific information. With this proviso, participants can decide at the outset of a study if they wish to participate in research or not. Those who are completely opposed to being recontacted with medically relevant information could simply decide not to participate in research.

In summary, the Schupmann et al⁴ paper, in conjunction with changing standards of care in clinical genomics and new recommendations for global genomics research, provide a rationale for challenging the current perspective on the “right not to know.” We propose that all future genomic research projects should incorporate the return of results in some fashion. When research projects extend over years or decades, we cannot assume that participants’ perspectives on genomic information are static. Rather than asking research participants to provide a binary “yes” or “no” to receiving any secondary genomic findings at the time of the initial consent process, we suggest that participants should be alerted at enrollment that they could be recontacted in the future if medically important information were discovered. Attempting to recontact participants with actionable genomic findings should be the default process in every research project, and once contacted, incremental information could be provided, allowing participants to opt out of the subsequent evaluation process at any time. Taken together, these suggestions could provide new opportunities for returning life-saving genomic information to research participants whose initial decisions are uninformed or may change over time. Having defined a minimum set of unanticipated genomic information as actionable in the clinical realm, we should now apply this standard even more vigorously in the research realm.

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Conflict of Interest

N.B.G. declares no conflicts of interest. R.C.G. has received compensation for advising AIA, Genomic Life, Grail, Humanity, Kneed Media, OptumLabs, PlumCare and Verily and is co-founder of Genome Medical, a telemedicine company offering genetics expertise to patients, physicians, healthcare systems, and employers.

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