ESHG

COMMENT

Invited Commentary on "My Research Results: a program to facilitate return of clinically actionable genomic research findings" by Willis et al.

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European Journal of Human Genetics (2022) 30:256–257; https://doi.org/10.1038/s41431-021-01003-8

Willis et al. are to be congratulated and encouraged for their work in establishing a program that can provide secondary findings (what they call additional findings) to research participants undergoing exome or genome sequencing [1]. In this program they have grappled with the many challenges of secondary findings in the research setting and developed a program that balances research and clinical obligations to participants, respects the widely held view of participants that they wish to receive such results, and addresses a key limitation, which is that few researchers have the expertise or capability to manage such findings themselves. They have done this by establishing a national program that connects participants to a centralized and uniform process with thoughtful oversight. This program has similarities to the proposed Australian program for secondary findings in clinical sequencing and to a program established by us in the Intramural NIH Research Program for research sequencing [2], but also some key differences.

The My Research Results (MRR) program involves an initial opt-in consent at the time of sequencing (by the researcher) and a revisited consent at the time results are available (by MRR), with medical and genetic counseling and referrals to providers for evaluation and management of the finding. This two-stage process clearly has potential merit and is important to evaluate, but questions remain about whether such an intensive process is necessary or desirable. Interestingly, a recent study [3] of participant understanding of a similar consent process has raised substantive concerns about this approach, which is primarily designed to solicit preferences about the so-called 'right-not-to-know' genetic information about oneself. In that study, 8678 individuals elected to receive secondary findings, and 165 elected not to receive them. They invited all 165 SF decliners as well as a random sample of 330 SF acceptors to participate in a study to evaluate why participants made their original choice, and to give participants a chance to make a new binding choice. The startling finding was not only the tiny fraction of individuals who declined to receive the findings (1.8%), but that nearly half of them (46%) incorrectly believed that they had actually accepted the offer to receive the findings. Upon being given another chance to make a decision, nearly half of the original decliners changed their selection. These results call into question the wisdom of actively soliciting participant preferences to learn about secondary findings at the time of initial consent. What is critical is to recognize is that in practice (as opposed to the Schupmann et al. study [3]) if an individual opts-out initially, there will almost never be an opportunity for them to receive the results they may indeed want because no secondary finding will be identified. Asking all participants about their preferences will necessarily lead to the outcome that some of them will not receive a benefit that they otherwise would have wanted. The normative question is whether such a process is ultimately respectful of autonomy. It will be essential for the MRR program and the Australian clinical secondary findings program to carefully evaluate this potential unintended consequence of their program design.

The Australian approach stands in contrast to the approach in the European Society of Human Genetics statement [4]. In this 2020 statement, the ESHG states '…genomic analysis should be as targeted as possible…" and recommend delay of consideration of secondary findings (what they term opportunistic genomic screening). Their conclusion is that secondary findings should only be considered for pilot studies—"…if OGS is being offered, it should take the form of pilots combined with rigorous evaluation studies…". This tepid endorsement of pilot studies more than 7 years after the secondary findings issue first arose is striking in its conservatism.

In their statement, the authors devote a few paragraphs to the possible benefits of secondary findings but pages to hypothetical risks, which was to a degree preordained by the composition of the committee. The statement asserts that evidence for returning secondary findings is lacking. Yet, one could be forgiven for skepticism regarding this point. A striking example is the notion of psychologic distress. The policy statement asserts (six times) the oft-repeated hypothetical concern of psychologic distress. Three papers are cited with the dismissive note that "…some recent studies of the psychological impact of receiving 'positive' SFs were to some extent reassuring…" The authors neglected to note an overwhelming body of evidence for a lack of evidence for such distress in many genetic testing contexts [5]. If patients successfully adapt in other contexts, and preliminary data show [6] this is not an issue in secondary findings, why would they repeatedly cite such an unsupported hypothetical concern? In some ways, the statement has the appearance of a conclusion preceding the selection of supporting data. It is our highest duty to care for

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Received: 26 October 2021 Accepted: 1 November 2021
Published online: 22 November 2021

patients and if even a small fraction are distressed by what they learn, to care for their distress—not to avoid the care. Considering this issue more broadly, this entire line of thinking is a patronizing view of the psychologic resiliency of humans. In no other area of medicine do we withhold testing results from patients because of theoretical concerns, unsupported by (some might say contradicted by) data, that it might lead to distress.

The ESHG statement and the Australian clinical and research approaches to secondary findings form a stark contrast. The Australian clinical and research secondary findings efforts deserve encouragement and praise for their success in moving these programs forward. They are moving in a thoughtful and responsible way to use the best current available evidence to explore secondary findings, collect useful data to guide future policy, and discharge their duty to rescue and ancillary care obligations to their patients and research participants.

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ACKNOWLEDGEMENTS

The views expressed here are those of the author and may not reflect the views of institutions to which he is affiliated. The author is supported by NIH grant HG200387-08.

COMPETING INTERESTS

The author is an uncompensated member of the Illumina Medical Ethics Committee and receives honoraria from Cold Spring Harbor Laboratory Press. He receives salary from the National Institutes of Health and his spouse receives salary support from RTI Intl.

ADDITIONAL INFORMATION

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