Black participants in a genetic study were more likely to decline information about any unexpected disease mutations it found. AP PHOTO/DAKE KANG

Controversy flares over informing research subjects about 'incidental' genetic findings

By **Meredith Wadman** | Aug. 2, 2021 , 4:40 PM

Should people who volunteer for genomic studies be told about unrelated disease mutations that turn up in their sequence data? The decadeslong debate about such "incidental findings," which can include genes that boost risk for cancer or heart disease, flared up again last week after bioethicists at the National Institutes of Health (NIH) published **a study** showing many participants who at first refuse those findings can change their minds. Controversially, it went on to suggest all research participants should routinely be told about their genetic risks for conditions that can be prevented or treated—a change from current practice.

The controversy pits researchers, many of them physicians, who see incidental findings as an opportunity to boost the health of the millions who have had their genomes analyzed, against others, mainly bioethicists, who stress the need to respect study participants' hesitation about receiving information that might expose them to genetic discrimination or simply be unwelcome. Deepening the divide, the study showed Black participants were more likely to refuse incidental results. "That strengthens the argument for saying we've really got to get true consent, opt-in consent from everyone," says Susan Wolf, a lawyer who teaches health law and bioethics at the University of Minnesota Law School.

In the study, researchers re-contacted research participants in a large NIH study 1 to 3 years after they enrolled. Initially, 1.9% of participants had declined to receive incidental findings. The team reports in *Genetics in Medicine* that of the 83 initial refusers, 41 changed their minds and accepted after being presented with new information, including an assurance that researchers would only return results on genes that raised the risk for serious conditions that were preventable or treatable, such as cancer and heart disease. (Six participants who initially accepted the findings changed their minds and refused after being reapproached.)

"I had a hypothesis that we would have a surprising number of people who would be willing to change their mind, but I had no idea how strong that would be," says senior author Ben Berkman,

a lawyer who heads the section on the ethics of genetics and emerging technologies at NIH's Department of Bioethics. Notably, he adds, 46% of those who changed their minds misremembered, and thought they had consented at the get-go.

In current research studies that offer to return incidental findings, participants need to opt-in, affirming their desire to receive such results. Many bioethicists say the ability to actively choose whether to receive such results protects patients' rights to decide what information is generated about them and guard their privacy.

Berkman and his co-authors conclude instead that, given the number of minds that were changed during their study, an opt-out system would be better: Researchers should notify participants during the initial informed consent process that they will receive incidental results, and withhold the findings only if they actively refuse, the authors recommend. NIH itself appears open to that approach; **the press release** for the study announced, "New study brings into question current policies on receiving secondary genomic findings."

For Berkman, the issue is clear: The results could be lifesaving, spurring people to get medical care or early, preventive screenings against diseases like colon cancer. "There has been this hyperfocus on this small number of people who don't want this information," says Berkman, who is also the deputy director of the bioethics core at the NIH's National Human Genome Research Institute (NHGRI). "Should we really be making policy on the basis of the interests of this tiny group?"

In the study, however, Black participants were significantly more likely than others to refuse incidental findings, sometimes expressing distrust of NIH. They initially rejected receipt of secondary findings at twice the rate of white participants and were less likely to change their minds after being reapproached. That finding has intensified other bioethicists' qualms about automatically sending incidental results.

"This research makes a recommendation without any regard to the Black participants' answers," says Keisha Ray, a bioethicist at the McGovern Center for Humanities & Ethics at the University of Texas Health Science Center, Houston. "Why isn't this their recommendation: `Based on the answers and hesitation expressed by the Black participants and their fear that their genetic information will be misused by the NIH, we recommend that secondary genetic information should not be given to participants unless they directly consent to knowing?'"

Berkman responds that the small number of Black participants—57--makes him "wary of making a concrete policy suggestion without more data."

To bioethicist Faith Fletcher of the Baylor College of Medicine, the new study points to the urgent need for more research. She calls for "work to find out why participants refused and how we use information from the study to figure out ethically informed ways to handle secondary findings."

Leslie Biesecker, a clinical and molecular geneticist at NHGRI who was not involved with the study, says "This study specifically highlights the disadvantages of the check-box approach." Asking participants to simply check a box to opt in or out is "a lousy substitute for working together with participants in a thoughtful and flexible way." He also bemoans that the most common reason given for declining, offered by more than half of initial refusers, was that the information would make them "worried or sad." "I am aware of no other specialty in medicine that withholds potentially lifesaving information from patients because of a concern about the patient being worried or sad," he says.

To Robert Green, a physician-scientist and medical geneticist at Harvard University who was not involved with the new study, it is "stunning" that only a small number of research studies return incidental results in the first place. "There have been tens of millions of people around the world who have either been genotyped or sequenced for research. And only a tiny, tiny fraction of those have ever been offered the opportunity to have any of those results returned to them for their potential medical benefit." But he thinks the "zeitgeist" is changing. For instance, NIH's huge All of Us Study is returning incidental findings to those who opt in.

Green, Biesecker, and others **stirred controversy in 2013** when they published, for the American College of Medical Genetics and Genomics, **a list of more than 50 genes** that ACMG recommended should be tested in any patient undergoing genetic screening in a clinical setting, with the information automatically returned to patients. After a storm of pushback, **ACMG backed off**, saying patients should be allowed to opt out of receiving such findings.

One of the co-authors of the original ACMG list now calls the automatic return of incidental findings from research projects "a bridge too far." "Even though the number of people who did not want the results back is very small," says Robert Nussbaum, chief medical officer at Invitae, a medical diagnostics company, "do we want to `ride roughshod' over [them]? The answer to that is probably no."

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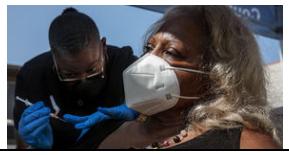

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