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Return of Results in Genomic Research Using Large-Scale or Whole Genome Sequencing: Toward a New Normal

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Abstract

Genome sequencing is increasingly used in research and integrated into clinical care. In the research domain, large-scale analyses, including whole genome sequencing with variant interpretation and curation, virtually guarantee identification of variants that are pathogenic or likely pathogenic and actionable. Multiple guidelines recommend that findings associated with actionable conditions be offered to research participants in order to demonstrate respect for autonomy, reciprocity, and participant interests in health and privacy. Some recommendations go further and support offering a wider range of findings, including those that are not immediately actionable. In addition, entities covered by the US Health Insurance Portability and Accountability Act (HIPAA) may be required to provide a participant's raw genomic data on request. Despite these widely endorsed guidelines and requirements, the implementation of return of genomic results and data by researchers remains uneven. This article analyzes the ethical and legal foundations for researcher duties to offer adult participants their interpreted results and raw data as the new normal in genomic research.

1. INTRODUCTION

WGS: whole genome sequencing

WES: whole exome sequencing

ACMG: American College of Medical Genetics and Genomics

gRoR: return of genetic or genomic results

IRB: Institutional Review Board

NHLBI: National Heart, Lung, and Blood Institute

NIH: National Institutes of Health

Large-scale genomic sequencing, up to and including whole genome sequencing (WGS) and whole exome sequencing (WES), is a powerful technology that is increasingly used in both research and clinical care. In 2012, the American College of Medical Genetics and Genomics (ACMG) extolled the clinical advantages of using WGS over traditional single-gene testing (2), and in the past decade, the use of large-scale genome sequencing in research has only grown. WGS is now applied in research with affected and healthy participants, in both clinical and population research (102, 113). Such large-scale sequencing is used in primary research involving direct contact with participants as well as research on banked biospecimens and archived data that may be linked to the source individuals or deidentified (34, 44, 107).

Both WGS and WES involve detailed sequencing of the source individual's entire gene-coding region, generating a wealth of data that can readily be interpreted to identify disease-associated variants. In hypothesis-driven and disease-specific research, these results include findings on the genes and variants under study, plus findings on other genes and variants that are not the focus of the research. Terminology for the range of findings varies but commonly includes three categories: (*a*) research results on the genes and variants under study, (*b*) secondary findings when there is a roster of additional genes and variants deliberately analyzed for potential communication to the research participant, and (*c*) incidental findings that are beyond the research results and are not deliberately ascertained for potential communication (74, 120, 123). In practice, the terms secondary findings and incidental findings are often used interchangeably, and offering information in all three categories to research participants may be referred to as return of genetic or genomic results (gRoR). Indeed, distinguishing the categories is especially difficult in inductive research designs that are not hypothesis driven or disease specific, but instead generate large volumes of sequencing data for future analysis in multiple studies (120).

Offering research participants findings from analysis of their own genetic and genomic material has a long history. Writing in 1980, Reilly (87) argued that an Institutional Review Board (IRB) "should ask each investigator to describe three categories of disclosure," beginning with "findings that are of such potential importance to the subject that they *must* be disclosed immediately" (p. 5). In 1999, the National Bioethics Advisory Commission (75) recommended return of results in research involving human biospecimens when "the findings are scientifically valid and confirmed," "the findings have significant implications for the subject's health concerns," and "a course of action to ameliorate or treat these concerns is readily available" (p. vii). In 2001, a group convened by the Centers for Disease Control and Prevention noted that returning individual-specific results in population-based genetic research "may be appropriate" "[w]hen the risks identified. . .are both valid and associated with a proven intervention for risk reduction" (11, p. 2320). A group sponsored by the National Heart, Lung, and Blood Institute (NHLBI) at the US National Institutes of Health (NIH) offered similar recommendations in a 2004 conference (proceedings published in 2006) for return of genetic results when the risk of disease is significant, the disease involves "fatal or substantial morbidity or. . .significant reproductive implications," and "[p]roven therapeutic or preventive interventions [are] available" (15, p. 1033). The NHLBI convened a subsequent group to generate updated recommendations that were published in 2010 (36).

Meanwhile, the NIH began funding extramural research on gRoR, beginning in 2005 with a project on managing incidental findings in human subjects research (123). That project built on the more advanced empirical and normative work on incidental findings in imaging research to offer guidance for genetic research and resulted in the 2008 publication of a consensus paper presenting analysis and recommendations (123) as part of a symposium journal issue that included multiple related papers. Two subsequent projects from this group, which focused on gRoR in

research involving biobanks and data archives (120) and on return of genomic results to the relatives of research participants (118, 125), were part of a substantial increase in NIH investment of research funding for this important problem. Indeed, in 2010 and then 2012, the National Human Genome Research Institute (NHGRI) at the NIH solicited grant applications for its Clinical Sequencing Exploratory Research (CSER) program, funding multiple projects investigating gRoR (44). Additional NIH-funded research programs have involved gRoR as well [e.g., the NHGRI-funded Electronic Medical Records and Genomics (eMERGE) Network and the NHLBI-funded Population Sequencing Study of the Framingham and Jackson Heart Study participants] (37, 41, 50, 114). From the start of the *All of Us* Research Program (*AoU*) led by the NIH, the program made a commitment to genomic analyses with "responsible return of personal results" (82, p. 43; see also 33, 77). **Figure 1** provides an overview of the rise of gRoR in the United States.

NHGRI: National Human Genome Research Institute

CSER: Clinical Sequencing Exploratory Research

eMERGE: Electronic Medical Records and Genomics

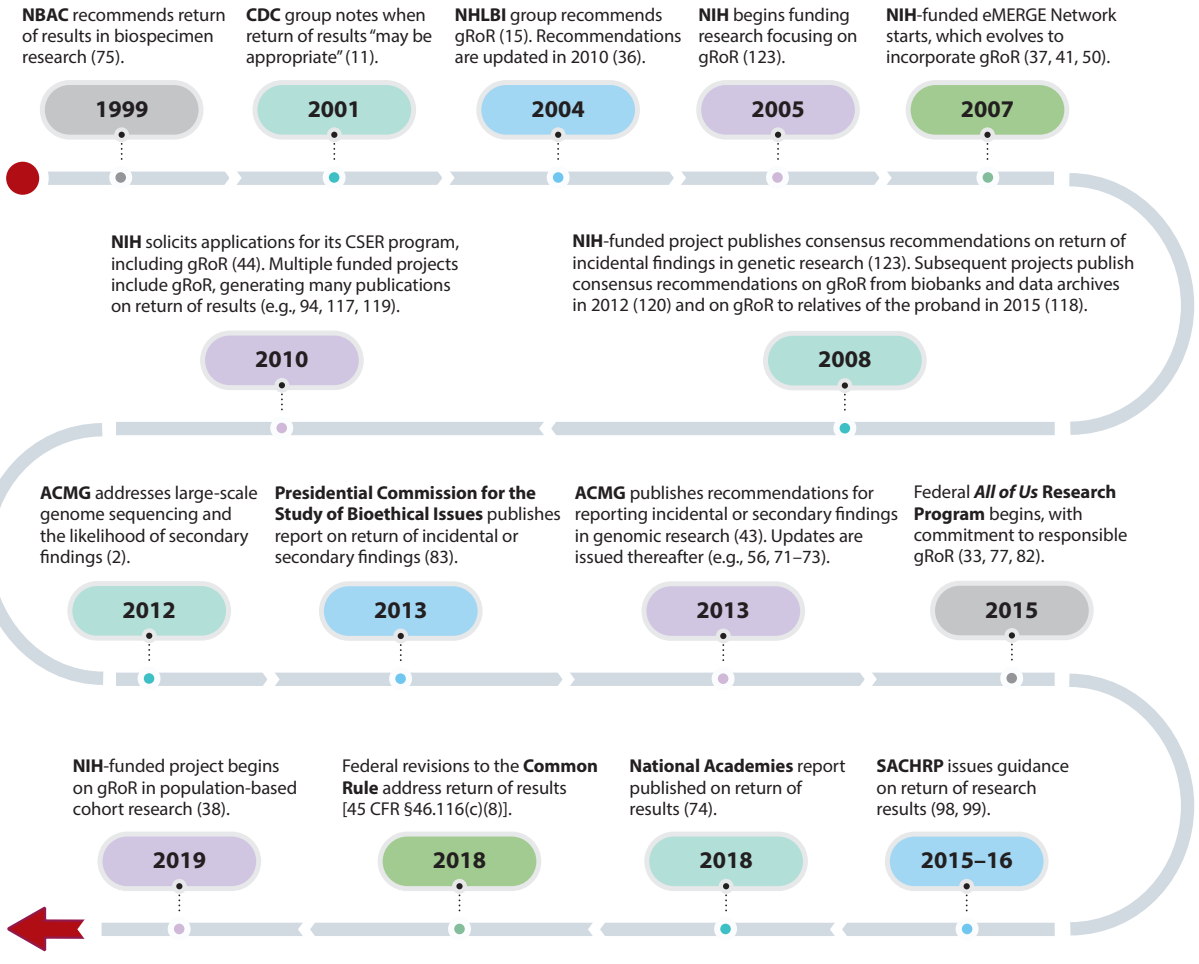

Figure 1

Timeline of key dates in the US development of gRoR in genomic research. Abbreviations: ACMG, American College of Medical Genetics and Genomics; CDC, Centers for Disease Control and Prevention; CSER, Clinical Sequencing Exploratory Research; eMERGE, Electronic Medical Records and Genomics; gRoR, return of genetic or genomic results; NBAC, National Bioethics Advisory Commission; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; SACHRP, Secretary's Advisory Committee on Human Research Protections.

AoU: *All of Us* Research Program

CMS: Centers for Medicare & Medicaid Services

FDA: Food and Drug Administration

SACHRP: Secretary's Advisory Committee on Human Research Protections

Growing interest in and attention to gRoR have given rise to a multidisciplinary literature analyzing the scientific, medical, ethical, legal, and policy implications of returning genetic results, both in the United States and across the globe. In addition to scholarly analyses and consensus group recommendations, multiple bodies have weighed in, including patient advocacy groups such as Genetic Alliance (108); professional societies such as the ACMG (3, 43, 56, 71–73); governmental authorities such as the US Centers for Medicare & Medicaid Services (CMS) and the US Food and Drug Administration (FDA) (35, 74, 113); federal advisory bodies such as the Secretary's Advisory Committee on Human Research Protections (SACHRP) in the US Department of Health and Human Services (98, 99); the National Academies of Sciences, Engineering, and Medicine (74); the Presidential Commission for the Study of Bioethical Issues (83); and international bodies such as the Global Alliance for Genomics and Health (39, 62, 110). In 2012, the director of the NIH called gRoR "one of the thorniest current challenges in clinical research" (60).

The rise of WGS as the increasingly standard technology for genomic research, and as a growing diagnostic path in clinical care, has made the challenge more acute. WGS guarantees that for many research participants, findings of potential health and personal importance will be present within the sequence if investigators take the trouble to find and report them. In 2012, the ACMG (2) declared that large-scale genome sequencing would yield "diagnostic results" in many cases, and that "secondary findings are highly likely, if not inevitable, whenever WGS/WEG is performed" (p. 759). This means that WGS holds great promise to generate useful results, but with a frequency and volume that can make gRoR a challenge. Responsive analyses focusing specifically on gRoR in WGS and WES have emerged (22, 58, 69).

In 2008, prompted by publication of the first two completed human genome sequences of known individuals, McGuire et al. (69) offered recommendations for gRoR and return of raw data in the WGS research context. They recommended that each project develop explicit policy, with training for physicians on communicating results. They urged entering into the participant's electronic health record "[o]nly validated data of known clinical relevance" (69, p. 153), with a process created to update that record as knowledge progressed. They also addressed gRoR for relatives of those being sequenced, relying largely on the participant to share information with family but leaving the door open to clinicians sharing information directly (even if unauthorized by the proband), "depend[ing] on the clinical relevance of the information and the potential to avert or alleviate known health risks" (69, p. 153). The issues of how to decide the scope of return, how to handle evolving genetic knowledge and potential need for recontact, and whether direct disclosure to relatives is appropriate continue to generate controversy.

In 2012, the ACMG (2) echoed the call for express policy for clinical WGS/WES: "Laboratories and clinics using WGS/WES should have clear policies in place related to disclosure of secondary findings. Patients should be informed of these policies and the types of secondary findings that will be reported back to them and under what circumstances. Patients should be given the option of *not* receiving certain secondary findings" (p. 760). The ACMG thus added an element that would later cause controversy—the idea that patients should have a choice as to whether to receive secondary findings. While this policy statement addressed the clinical domain, the recommendations had clear implications for the research domain as well, suggesting that genomic researchers should also address these issues.

Commentators began to focus on the dimensions of WGS in research that made gRoR more challenging than return of results and findings in projects using more limited analyses. First, in research using WGS, the scope of potential results and findings was extremely broad. Second, WGS could be deployed in assembling large datasets for use in future research; in that context, distinguishing research results from secondary or incidental findings was difficult, as no hypothesis

delimited the scope of research results at the time of initial sequencing (80, 106). Third, research laboratories performing WGS might generate findings "of low diagnostic quality" and might not use a laboratory compliant with the Clinical Laboratory Improvement Amendments (CLIA); consequently, "all research findings will require further confirmation and validation by experienced professionals in a clinically accredited laboratory" (48, p. 319). In addition, FDA Investigational Device Exemption regulations might apply (113). Despite these concerns, Tabor et al. (106) wrote that "it is no longer a question of whether or not results with clinical utility will be found in any research participant by. . .WGS, but rather how many such results will be identified in each participant" (p. 2920). Beyond that, assembly of a large dataset may mean that the number of participants for whom gRoR is considered could be so large that gRoR would be burdensome. Such concerns may have played into the decision by the UK Biobank not to return any genomic results (111) despite having array-based data, exome data, and ultimately WGS on nearly half a million participants.

CLIA: Clinical Laboratory Improvement Amendments

These concerns warrant specific consideration of gRoR in the context of research using WGS. The goal of this article is to analyze grounds for gRoR, distinguish the considerations that apply to return of raw data, address concerns, and suggest a path forward. We clarify why momentum in the direction of gRoR is growing, yet confusion persists on the underlying ethics and law. This article focuses on gRoR in research with adults; the rich literature on gRoR in research with children and adolescents warrants its own treatment. We also focus on gRoR in US research; though gRoR has gained considerable traction outside the United States, jurisdictional differences in law as well as ethics call for separate consideration internationally.

The widening incorporation of gRoR in contexts ranging from the CSER Consortium and eMERGE Network to large population studies such as the Framingham Heart Study, Jackson Heart Study, and *AoU* signals that gRoR is increasingly part of the new normal in research (37, 41, 44, 50, 55, 77, 114). Many biobanks now incorporate gRoR for medically actionable genes (26, 129). A consensus committee of the National Academies of Sciences, Engineering, and Medicine recommended in 2018 that "investigators. . .routinely consider whether and how to return individual research results" (74, p. 11). Though the Common Rule governing research with human participants has long addressed discovery of "new findings developed during the course of the research that may relate to the subject's willingness to continue" [45 CFR §46.116(c)(5)]—which arguably applies to participant-specific findings (124)—the 2018 revision to the Common Rule now expressly addresses investigators' obligation to state "whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions" [45 CFR §46.116(c)(8)]. Meanwhile, surveys reveal overwhelmingly that participants expect to be offered their findings (19, 70, 101, 112), and behavioral studies indicate that participants who elect to receive gRoR generally experience very limited psychosocial distress (24, 49, 94, 100).

Return of results and incidental or secondary findings has been successfully integrated into multiple domains of research beyond genomics, including neuroimaging and environmental health research (16, 17, 52, 74). Making gRoR a standard and expected practice in WGS research is equally important. Indeed, the growing power of WGS to reveal health risks and the related opportunities for clinical intervention make gRoR in WGS an opportunity to generate highly valued knowledge that can advance health and save lives.

2. RATIONALE FOR RETURN OF RESULTS IN RESEARCH

Offering research participants their own genomic results rests on a cluster of ethical and legal considerations articulated below. It also rests on copious empirical data demonstrating the interest

of participants in receiving these results and on a sea change in the culture and expectations in research. Increasingly, researchers and oversight authorities have recognized the importance of considering participant expectations and treating participants as essential partners in research rather than "passive, disenfranchised purveyors of biomaterials and data" (59, p. 837).

2.1. Empirical Grounds

Multiple studies have found that research participants expect to be offered their research results. In an early study of research participant preferences with regard to disclosure of incidental genetic findings, most wanted disclosure of all incidental findings, regardless of actionability (54). Likewise, a comprehensive literature review from 2010 to 2016 showed that a majority of participants wanted to receive both actionable and nonactionable secondary genetic findings (32). Though studies show that most people expect to be offered their genetic results, they also show that some participants decline the offer, either passively (e.g., by not responding to a phone call or letter) or actively (by responding but saying no) (129). Rates of passive and active decline vary, often reflecting differences in protocol design for offering and returning results. However, it is not surprising that participants would overwhelmingly support the idea that they should be offered their own results and then would make a more nuanced decision when actually offered their results. By the time they are actually offered such results, participants may be coping with more acute health concerns or may have already learned of the result through their own healthcare. Indeed, one study showed that "individual experience and life context (circumstances) were decisive in participants' expectations and fears regarding access" to their results (51, p. 1).

Other studies show that participants may decline results out of fear of the psychological consequences of receiving their results (7, 51, 103, 127). However, studies of participants who do elect to receive even potentially frightening results—such as an *APOE* e4 variant signaling an elevated risk of Alzheimer's disease—are reassuring (23, 46, 91–93). One study showed that anxiety and depression did not increase significantly after results disclosure, finding "low levels of test-related distress and perceptions of uncertainty. . .and a wide range of positive responses" (94, p. 2781).

Against this background, it is important to examine the ethical and legal rationales for return of results, as both have sometimes been misunderstood (35).

2.2. Ethical and Legal Grounds

The question of whether to offer research participants their individual-specific data, results, and incidental findings has long been recognized. In 1980, Reilly (87) published an article entitled "When Should an Investigator Share Raw Data with the Subjects?" arguing that there were indeed instances that merited sharing information. Starting in 1999, multiple consensus guidelines have supported return of results and incidental or secondary findings. The 1999 guidelines authored by the National Bioethics Advisory Commission (75) addressed duties to individuals whose biospecimens were archived for research use. The commission recommended returning results only when "the findings are scientifically valid and confirmed," "the findings have significant implications for the subject's health concerns," and "a course of action to ameliorate or treat these concerns is readily available" (p. vii). Recommendations since then have echoed these criteria, including recommendations from a group sponsored by the Centers for Disease Control and Prevention in 2001 (11) and recommendations from NHLBI working groups published in 2006 (15) and 2010 (36). A series of NIH-funded working groups elaborated these guidelines further in generating recommendations for managing incidental findings in genetic research (123), handling return of results and incidental findings in research involving biobanks and data repositories (120), and determining whether to offer results to relatives, including after the death of the research participant

(118, 125). Other groups have offered guidance as well (22, 57, 62). In 2018, a report from a committee at the National Academies of Sciences, Engineering, and Medicine on returning individual results to research participants urged that "investigators and their institutions should routinely consider whether and how to return individual research results" (74, p. 11).

Multiple ethical grounds support these recommendations. A fundamental duty to respect the autonomy and decision-making of research participants calls for transparency on the range of data to be collected from them, the analyses to be undertaken and type of results to be generated, whether those results may hold health significance, and how such results will be handled. Indeed, the federal Common Rule governing research with human subjects was revised effective 2018 to add a new element of informed consent: "[a] statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions" [42 CFR §46.116(b)(8)]. Without such transparency, individuals cannot make an informed decision on whether to participate in the research.

Respect for autonomy also calls for sharing information that might influence participants' decision about whether to continue research participation or withdraw. Alerting a participant about a finding that raises potential health concerns may indeed affect their decision on whether to continue or instead devote their energies to clinical evaluation of the finding. Again, the Common Rule recognizes the need for transparency, providing that an additional element of informed consent is "[a] statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject" [42 CFR §46.116(b)(5)].

Broader respect for a participant as a true partner in research rather than as a mere means to generating research findings also supports the notion that investigators should offer to share information generated that may be important to the individual (59). Research on human genomics is not possible without the generous willingness of individuals to participate and contribute their biospecimens. This has led some analysts to identify ethical duties of reciprocity and solidarity underlying researcher duties to offer back individual-specific results (52, 84). While some biospecimens may be collected and analyzed in research protocols that fall outside the definition of human subjects research covered by federal regulations (e.g., when collected in clinical care and then deidentified for research), researchers should anticipate that even these may generate findings calling for consideration of recontact and an offer of findings. An example is discrepant diagnosis—discovery by biobank pathologists that a specimen submitted as an example of a certain cancer or other disease was misinterpreted, raising the possibility that the source patient was misdiagnosed and is being treated for the wrong illness (64).

The idea that researchers owe some duty of clinical care has been most prominently articulated by Richardson and Belsky (88–90). They have argued that clinical researchers are not mere scientists with no duty of care, but neither are they clinicians with a full-blown duty to care for the participant as a patient. Instead, researchers occupy a middle ground. Because the participant entrusts the researcher with a certain degree of access to their body and confidential medical information—what these authors call "partial entrustment" (90, p. 27)—the researchers owe a duty of ancillary care. That duty then creates obligations to offer participants information in the researchers' possession that participants may reasonably want, expect, and need to take care of their health.

Finally, return of results and disclosure of incidental or secondary findings have been based on a duty to warn the participant in order to avert harm (10, 61, 74, 105). Here again, the idea is that a researcher with information that could be used by the participant to avoid harm has a duty to offer that information. For example, if a researcher discovers that a participant has a genetic variant that increases the risk of a serious illness (such as a cancer), and knowledge of the variant would

HIPAA: Health Insurance Portability and Accountability Act

allow the participant to lower the risk (for example, through earlier or more frequent screening), then the researcher has a duty to warn. Indeed, Berkman and colleagues (9, 103) have argued that researchers can ethically design their protocols to make return of certain results the default option (rather than first asking participants if they want their results) as long as they provide an opt-out mechanism for participants who wish to decline the information. One of the few legal cases to date that has considered researchers' duties to offer results rested on the duty to warn. In the *Grimes* case (47), parents sued researchers who were studying the effects of different degrees of lead paint abatement in Baltimore housing, complaining in part that researchers failed to promptly alert parents to their children's elevated lead blood results. The decision of the Maryland Court of Appeals has been questioned on other grounds, but it highlights researcher duties to warn.

Researcher duties to offer findings of importance to research participants thus rest on a cluster of ethical concepts, as well as regulations protecting human subjects and case law indicating that research participants can bring claims for failure to offer this information (124). Unfortunately, the grounds for these duties have sometimes been misunderstood. For example, an appendix to the National Academies report on return of results purports to analyze the ethics literature by asking, "When, if ever, is returning results. . .morally imperative for all human subjects research. . .?" (74, p. 340). This question is misleading. The ethics literature has not argued that return of results is "imperative" across "all" research with human participants. Instead, the literature differentiates scenarios when researchers should return, may return, and should not return results (36, 120, 123) and recognizes circumstances in which return of results is impractical (for example, due to limits on resources, lapse of time, or difficulty relocating participants) (27, 48, 126).

As a growing number of research projects incorporate return of results—including large-scale projects with genomic analysis, like *AoU*—funders, research institutions, IRBs, and research participants increasingly expect that researchers will offer results. In addition, tools are emerging to simplify and routinize return of results, such as research use of the ACMG's roster of secondary findings recommended for return in clinical sequencing (43, 56, 71–73, 79). The NIH has funded multiple major research consortia incorporating and studying the return of genomic results, such as the CSER Consortium (44) and eMERGE Network (37, 41, 50, 114). Even the NHLBI's large Trans-Omics for Precision Medicine (TOPMed) Program, which comprises more than 80 studies, includes studies returning results (38, 55, 104) and has posted draft guidance on gRoR from its Ethical, Legal, and Social Issues Committee (76). All of this is contributing to a shift in research practice toward return of results.

3. DIFFERENTIATING ACCESS TO RAW DATA

A common misunderstanding is to confuse return of interpreted results with research participant access to their raw data. The latter is largely governed by the federal Health Insurance Portability and Accountability Act (HIPAA), though state law can provide additional access rights. Evans & Wolf (35) have carefully differentiated the two practices, which have different contours, histories, and legal foundations. Access to raw data under HIPAA is an aspect of individuals' rights to see the content of their dataset, in order to make informed judgments about authorizing release and sharing of those data. Access also allows participants to consider other uses, such as contributing their data to additional research projects (121).

The HIPAA Privacy Rule, finalized in 2000, incorporated from the start a right of access to one's own data. As Evans & Wolf (35) explained, this right was originally limited in some states by laws restricting access to laboratory results. However, in 2014, the federal government promulgated a new rule that preempted state law and removed those limitations. This vindicated a right long deemed central to privacy—the right to see and obtain one's own data when they are being held by another: "Unless people can see the information being stored about them, they cannot assess

how much privacy risk the information may pose. Are the data embarrassing? Is their storage or circulation a source of concern?" (35, p. 1303).

Genomic data can be sensitive, revealing personal and family health risks or uncovering misattributed familial relationships. The privacy risks multiply when the data being held represent an individual's entire genome. Federal and state laws protecting against genetic discrimination are only partial protections; they fail to fully eradicate risks of stigma and penalty based on genetics (25, 45, 96, 97). The risks extend beyond healthcare and insurance to use by law enforcement authorities and immigration authorities (67, 85).

The HIPAA right of access to one's data is distinct from return of results (35, 65, 109). The former entitles people "to inspect and make copies of all of the data about themselves that a HIPAA-covered entity (such as a hospital, clinic, or HIPAA-regulated laboratory) has stored in each person's designated record set" (35, p. 1304). This can include access to research records and raw genomic data (35). Once an individual requests their records, prompt fulfillment of the request is required to avoid potential administrative and civil penalties. However, HIPAA requires no interpretive assistance, only provision of the records.

A task force of the Global Alliance for Genomics and Health found that the majority of research participants surveyed wanted the right to access their raw genomic data. The task force generated recommendations that included "[p]rovide access to genomic data in standard formats" (109, p. 4), listing FASTQ, Binary Alignment Map (BAM), and Genome Variant Call Format (gVCF). Importantly, they called for researchers to "[d]escribe the right of access in the consent form" and "[d]istinguish [the right of access] from the plan for return of individual findings of clinical relevance" (109, p. 4). Many research participants are likely to be oblivious to this right of access unless informed.

In keeping with legal and attitudinal support for providing research participants access to their raw data, Lunshof et al. (65) have articulated ethical arguments. Offering access "is a basic requirement for a just and reciprocal relationship" (65, p. 373) characterized by transparency. Such access also supports the individual's agency by giving them the choice of what to do with their data, such as the option of seeking independent analysis and interpretation. Finally, it provides individuals the opportunity to contribute their data to other research efforts. Without such access, data sources are kept in the dark while researchers, data repositories, and often waves of secondary researchers utilize their data.

4. PROCEDURES FOR RETURN OF RESULTS AND THE SCOPE OF RESULTS TO RETURN

When researchers decide to offer interpreted results with health implications, the specimen chain of custody and analytic validity of the results may not match the standards required by clinical laboratories. Filtering, interpretation, and reporting of genomic variants by a research team may not follow the standards used in clinical laboratories and thus may call for confirmatory testing or act as an alert, prompting referral to clinicians for evaluation of the finding in the context of fuller genetic and phenotypic examination, including family history. Return of results is thus an intrinsically translational process—a handoff from the research context to the clinical one (116, 119).

Some commentators have suggested that no research results should be returned unless they meet or approximate the same standards required of clinical laboratory findings (74). This position fails to appreciate the function of return of research results, as an alert to prompt repeat testing and clinical evaluation rather than as a substitute for that evaluation. Research and clinical care are thus interrelated but fundamentally different domains, pursuing different goals (generalizable knowledge versus care of the individual patient), governed by different standards (including

laboratory standards accommodating discovery in domains not yet well understood versus CLIA standards for laboratory practice), and with different financial constraints (research budgets versus payment systems for clinical care) (116).

Given the differences between these two domains, return of results in the research domain serves multiple purposes. It can alert research participants to potential problems that would benefit from clinical workup to confirm and address the problem or rule it out. Return of results can also allow researchers to study how to best offer and communicate potentially important findings discovered in research and how to best perform the handoff to clinical care—one goal of NIH-funded projects in the CSER Consortium (44). Return of results also plays a translational role, prompting researchers to develop laboratory and genetic counseling protocols to address a finding, thus paving the way for the development of appropriate clinical protocols to address that finding when those protocols are not yet fully developed (119).

In the future, more investigators may collect research specimens with the same standard for identity confirmation and chain of custody, as well as equivalent standards of interpretation and reporting, as those employed by molecular laboratories that receive medical specimens, thus obviating the expense and logistics needed for specimen recollection and retesting.

4.1. Analytic Validity, Clinical Validity, Clinical Laboratory Improvement Amendments, and Food and Drug Administration Compliance

From their initial emergence in 1999, guidelines on return of results have recommended that the results offered to research participants should be "scientifically valid and confirmed" with "significant implications for the subject's health concerns" and that "a course of action to ameliorate or treat these concerns [should be] readily available" (75, p. vii). The precise statement of these requirements for analytic validity, clinical validity, and actionability has varied, but all are commonly stated recommendations.

Specifying how each requirement should be met has prompted controversy. We address the actionability debate below. Debate over analytic and clinical validity has centered on the question of whether research results need to meet clinical standards and whether such a result should be generated in a CLIA-compliant laboratory to qualify for return to the research participant. While some genetic and genomic research is already conducted in CLIA-compliant laboratories generating results and laboratory reports with variant interpretation that meet clinical standards, much research is not, for good reason (35, 74, 117, 121). Researchers, including those conducting WGS, may be sequencing and investigating genomic phenomena that are not yet fully understood. Researchers may use a research laboratory rather than a clinical one for additional reasons, including the need to avoid the higher cost associated with laboratories or workflows that are CLIA certified.

However, the mere fact that analyses are conducted in a research laboratory instead of a clinical one does not necessarily indicate lower analytic and clinical validity. Research laboratories may maintain excellent and even superior quality controls that provide strong analytic validity. And the selection of genes and genomic variants considered for return may have well-established clinical implications.

Much debate has surrounded the question of whether results must be ascertained in a CLIA-compliant laboratory in order to qualify for return. A number of published guidelines finesse this question by calling for compliance "with all applicable laws" (36, p. 575) or expressly with CLIA, without spelling out what this requires. The 2018 National Academies report (74) added to the confusion. That report assumed that an unsigned post on the CMS website in 2014 required use of a CLIA laboratory for all results that might be disclosed to individuals. At the same time, the report recognized three established strategies for compliance with CLIA: (*a*) use of a CLIA

laboratory for the research; (*b*) use of a non-CLIA laboratory for research, with researcher confirmation of results being considered for return in a CLIA laboratory; and (*c*) return of non-CLIA results with a clear warning to the participant that the results should not be used for diagnosis or treatment and a recommendation that the participant consult a clinician for CLIA confirmation and clinical evaluation (35, 74, 121, 122). In an analysis that avoided the questionable assumption in the National Academies report, SACHRP confirmed the availability of all three strategies and their compliance with CLIA. Wolf and Evans (35, 121, 122) have similarly explained that all three strategies comport with federal law. Nonetheless, verbal communications from CMS representatives and conservative interpretations by research IRBs have led some in the field to assume that only results from a CLIA laboratory can be shared with participants.

Another important issue is the potential need for an Investigational Device Exemption under FDA regulations. Venner et al. (113) have described the process that *AoU* went through to obtain approval for return of results from WGS. This process began with an FDA determination "that the proposed project met the criteria for a Significant Risk (SR) Device Study" (113, p. 2) under 21 CFR part 812. The FDA thus required that *AoU* obtain an Investigational Device Exemption, which was demanding and time-consuming. While *AoU* is not the only research project to face this FDA requirement, the massive scale and public nature of *AoU* "presented a unique set of challenges" as well as "an opportunity to establish precedents for the genomic medicine research community" (113, p. 2).

4.2. Actionability

The early National Bioethics Advisory Commission recommendation that results considered for return show clinical actionability was the first of many guidelines conditioning return on actionability (36, 53, 75). The commission defined actionability to mean that "a course of action to ameliorate or treat these concerns is readily available" (75, p. vii). Fabsitz et al. (36) recognized that prevention constituted actionability as well, defining a finding as actionable if "there are established therapeutic or preventive interventions or other available interventions that have the potential to change the clinical course of the disease" (p. 575).

A range of views has emerged on what constitutes actionability (40). The clinical actionability definition advanced by Fabsitz et al. (36) is the narrowest but the most common. The ACMG (4) has recognized that the clinical utility of genetic and genomic tests is considerably broader, whether the testing is indication based or part of a screening effort such as newborn screening: "Arriving at a precise diagnosis always has the potential to lead to a change in medical management. . .even when directly preventing or lessening complications is not possible. For example, an etiologic diagnosis prevents additional unnecessary testing, provides the opportunity for anticipatory guidance, and provides better information regarding recurrence risks for the family and the affected individual" (p. 506). Moreover, terminating or avoiding a burdensome diagnostic odyssey and facilitating access to support services can be high-impact benefits (8).

The ACMG (4) also recognizes that sharing genetic and genomic information "[e]nables specific and informed reproductive decision-making and family planning" (p. 506). While some recommendations for return of results have treated results of reproductive actionability as among those that should be offered to research participants (123), others have not. Yet the consequences of deprioritizing or excluding reproductive actionability can be severe for women who undertake pregnancy and gestation and for families that initiate reproduction without access to genetic information that could alter their approach to building a family. Sharing such findings with research participants can alert them to the need to consider clinical testing and genetic counseling on their reproductive plans, as well as interventions such as preimplantation genetic testing and prenatal

testing. For women who might otherwise face difficulty conceiving and carrying to term, or who might face a difficult decision about whether to terminate a pregnancy, some types of genetic information would be more than just reproductively actionable. The return of these results could allow them to consider steps to minimize their clinical risk and protect their own health. The failure to regard reproductive actionability as a species of clinical actionability ignores a critical dimension of women's health (40, 115).

A third and broader dimension of actionability is personal utility. This ranges from "satisfying curiosity, to allaying anxiety, to communication with other family members, to purchasing insurance" (8, pp. 107–8). Participants can take action on results by educating themselves on particular diseases, mentally preparing themselves for a potential diagnosis, and making adjustments to their long-term insurance, housing, and financial plans. Participants may also decide to volunteer for further research on genes and diseases of concern. Definitions of actionability vary among stakeholders (66), and a growing body of research shows that a majority of participants want results that offer personal, as well as clinical, utility (8, 13, 54). In delimiting the scope of actionable findings and what results will be offered to research participants, researchers thus face the question of whether to define actionability from the standpoint of a clinician or a research participant. The National Academies report on return of results (74) urges researchers to respect the perspective of participants, which may support a broader scope of return (13). Broadening the scope of return may raise questions about the resources the research project can devote to this process, but it also suggests that researchers should ascertain the marginal costs of wider return and innovate to streamline the process of offering and returning results (86, 129).

4.3. Return of Results to Relatives

When researchers sequence a participant's genome, they generate information of potential importance not only to the research participants but also to the genetic relatives of those participants. Because genomic data may be archived in databanks or banked with biospecimens over long periods of time for use by secondary researchers, relatives may seek access to the results after the participant loses decisional capacity or dies. Researchers themselves may question whether they have duties to reach out to relatives with genetic information that could trigger cascade testing of family members and genetic counseling, especially if the research participant is unable or unwilling to alert family members.

In the context of clinical care, there is a long history of guidance from professional societies as well as litigation (and even state legislation) on whether clinicians have duties to alert family members (118). The dominant view is that clinicians are obligated to respect the confidentiality of patient information. When genetic results have implications for the health of family members, clinicians should urge the patient to share the information and can offer to assist by supplying a report or letter that can be shared, or being willing to meet with relatives. However, when the patient declines to share the information with family, the clinician should not be compelled to breach confidentiality by reaching out directly to family members. Only when the patient has refused to offer the information to family members, the clinician can identify those individuals at risk, and sharing is likely to avert significant and near-term harm may the clinician have a privilege (though not a duty) to share with relatives (6, 118).

In the research context, where the results may not be of clinical quality and the researcher may have no direct interaction with the participant or family (depending on the research design), the grounds for reaching out directly to family are weaker than in the clinical context. In addition, family members may already have some access to research results, as HIPAA allows a physician to share information with the relative's physician at the latter's request when necessary for the relative's treatment, though controversy persists over the appropriateness of such disclosure to

relatives (95). Additional HIPAA provisions may also offer relatives some access, such as the rule that after the individual's death, their personal representative (who may be a relative) makes decisions about sharing the individual's personal health information (118). An NIH-funded project devoted to developing consensus guidance on return of research results to relatives, including after the death of the participant, thus recommended that researchers should generally refrain from reaching out directly to family members and instead support the research participant, and then their personal representative, in responding to family requests for information (118, 125). The majority of those authors concluded that only in exceptional circumstances, when the participant (or personal representative) declines to alert specific family members at risk and sharing results is highly likely to avert imminent harm, should researchers consider initiating contact with relatives to offer the results.

Because genomic information often has implications for relatives and may be archived for secondary research, investigators should address in their research protocol how they plan to handle potential return of results to relatives. Researchers should elicit participant preferences on sharing their results with relatives in the future, including what to do if the participant loses decisional capacity or dies (118, 125). Empirical research indicates that most participants are likely to authorize sharing (at least in populations studied to date) but that some participants prefer not to share (18, 42). Participants may also wish to designate a specific relative to receive their results or act as their personal representative to make decisions about sharing (5, 118, 125). Developing a protocol for return of results to relatives is especially important in cancer and other disease-based research where participants are at elevated risk of dying before they have the opportunity to receive their results or share them with relatives (7, 118, 125).

5. CHALLENGES

While the principles underlying return of results and incidental or secondary findings are now well established, best practices are still being refined and challenges remain. Among those challenges are ensuring that return of results advances health equity, that procedures for return of results can accommodate advances in genomic knowledge leading to variant reinterpretation, and that the entire process is feasible given constraints on research budgets.

5.1. Health Equity and Inclusion

For return of results to advance health equity, the practice needs to respect the preferences of historically underserved and minoritized populations, provide valuable information, and advance well-being. A number of studies have examined preferences. For example, Joffe et al. (55) found that the majority of African American and white participants in the Jackson Heart Study and Framingham Heart Study wanted researchers to inform them of secondary findings. Yu et al. (128) conducted focus groups and found that both African Americans and non–African Americans wanted to receive clinically actionable results but that the former group "expressed concerns about a lack of access to health care that would limit their ability to follow up on actionable results" (p. 1067). Abul-Husn et al. (1) studied return of results in a multiethnic biobank based in the Mount Sinai Health System, finding that the vast majority of participants wished to receive their results. While most wanted results to help themselves and their families, more than half of respondents indicated that concerns over discrimination would be a reason not to receive results.

Achieving equity in return of results requires facing barriers to benefit for underserved and minoritized populations. As many scholars have noted, populations of non-European ancestry are underrepresented in genomic research and the resulting databases (1, 20, 63, 78, 81). Because some risk variants and genetic diseases vary in prevalence by ancestral group, the failure to include

adequate numbers of individuals of non-European ancestry can lead to omission of variants important in those populations (1) or misunderstanding of the clinical implications of identified variants (68). Correcting this bias in genomics is a priority that can advance equity in return of results. Indeed, "including medically actionable genomic conditions with higher prevalence in non-[European ancestry] populations can be an effective tool for expanding genomic medicine applications to historically underrepresented patient populations" (1, p. 9). In 2022, the ACMG and its Secondary Findings Working Group (71) took an important step toward advancing health equity by adding a gene to their secondary findings list that has a variant which is particularly common among individuals of African ancestry and can cause heart failure, writing, "To foster equity, the working group is committed to identifying genes and genetic variants that disproportionately affect diverse, historically underrepresented populations in an effort to reduce health disparities" (p. 1412).

In addition to research participants of non-European ancestry, any participants without ready access to healthcare face barriers to realizing the full benefits from return of genomic results. Sullivan & Berkman (105) have argued that researchers retain obligations to return results in low-resource settings where participants may not have easy access to clinical care, as individuals may have ways to obtain access to care, access could improve over time, and return of results could spur the individual or local community to advocate for improved access. They also point out that research funders could build into grants and research budgets adequate resources to provide needed genetic counseling and that research institutions could collaborate to centralize necessary resources. To advance health equity and inclusion, researchers and their institutions should plan for participants without health insurance and established clinical care in order to create referral pathways and provide required support (123).

5.2. Reinterpretation and Recontact

Rapid progress in genomics poses a challenge to research projects planning for return of results. In a proposed protocol, the team may specify a set of findings to be offered to research participants, which may be based on pathogenicity and actionability. However, the team may later find that the medical community's progress in understanding genomic variants suggests an expanded or modified list. For example, research projects using the ACMG list of secondary variants to delimit the set of findings for return have had to consider how to respond to periodic updates. That list initially consisted of 56 genes, but grew to 59, 73, and then 78 (43, 56, 71–73). The ACMG plans to update the secondary findings list annually (71, 72).

The ACMG secondary findings list was devised for clinical genome sequencing but has been used in research projects as well. In both clinical and research genomics, advancing genomic knowledge and clinical practice will raise questions about the need to reinterpret genomic variants and possibly recontact individuals with updated information (14, 21, 29, 31). In research, advances in knowledge may suggest expanding the list of findings to return, contracting the list, or modifying counseling on the implications of the results being returned. In 2019, the American Society of Human Genetics issued guidance on investigator responsibilities to recontact research participants if research results were reinterpreted (14). The authors strongly recommended trying to recontact the participant within six months of the reinterpretation when the reinterpretation was "related to the phenotype under study or. . .reasonably expected to affect. . .medical management" (14, p. 584). When the reinterpretation will not change management, they nonetheless advised trying to recontact the participant to correct a variant classification already reported to the individual when the change is "from or to pathogenic or likely pathogenic" (14, p. 584). However, the reality is that research projects often lack budgets and infrastructure for initial return of results, much less reinterpretation, recontact, and updated disclosure.

The American Society of Human Genetics guidance (14) urged research projects to address in their protocols both initial return of results and possible reinterpretation and recontact. This guidance recommended informing research participants that current variant interpretations may change with progress in knowledge and asking participants to consent to a plan that addresses both initial return of results and later recontact if necessary and appropriate. It also called on research funders "to encourage and financially support researchers' efforts to recontact participants in light of re-classified variants" (14, p. 591).

5.3. Resource Constraints

Logistical challenges can impede the return of results in research involving large-scale sequencing, including WGS and WES. Though some commentators voiced early concerns over cost (12), researchers now are reporting and analyzing cost more systematically (129). Cost may vary considerably by research design, the scope of findings offered, and the participant population. Studies have explored methods to control costs, including by offering a computer interface for participants to select findings they wish to receive (59). Another approach that may be especially useful when only a limited subset of a large biobank or research population will likely have findings that warrant return is to offer return of results in stages; while all participants should be consented for a protocol that may involve return of results, only those with relevant findings may need more detailed, incremental consent for return of those results (129).

Research studies can legitimately take a range of approaches to return of results, including whether they offer any return at all, and if they do, whether they include CLIA confirmation of results and genetic counseling in the research process or instead hand off those functions to a clinical team (117). Where a research team draws the line between research and clinical activities will clearly have implications for cost and personnel requirements. Some researchers may not have the proper background or training to return genomic results directly to participants. To address this issue, Darnell et al. (28) proposed a "secondary-genomic-findings service (SGFS) that would support researchers by enabling the return of clinically actionable sequencing results to research participants in a standardized manner" (p. 435). Further research and innovation will clarify options for return of results and the associated costs.

6. CONCLUSION: TOWARD A NEW NORMAL

More than two decades of multidisciplinary research, consensus projects, and professional society guidelines now support and shape the practice of offering research participants their genomic results, including secondary and incidental findings. At the same time, the regulations on human subjects research have evolved to recognize the importance of addressing return of results in planning research and then disclosing that plan to prospective participants to inform their decision about whether to enroll. Indeed, consulting the participant community in advance to collaboratively devise the approach to return of results is increasingly part of research projects, such as *AoU* (33) and the Kidney Precision Medicine Project (30).

Large-scale genome sequencing is virtually guaranteed to generate findings that should be considered for return to some participants, given the scope of the data collected and analyzed. The days when investigators could ignore the question of what results to offer to participants have passed. Not all projects will be able to return results; those working with deidentified data collected long ago, with no tracking of participant contact information and no systematic way to ascertain whether the genetic risk has already eventuated in illness or death, are least likely to be able to offer results and to confer benefit by doing so. Retrofitting projects and biobanks that were not designed or consented with return of results in mind is especially challenging (120).

Prospectively, funders, IRBs, and participants increasingly expect projects and biobanks to consider the return of results in their plans and protocols. The last two decades have witnessed a sea change in research, advancing toward greater partnership with participants and respect for their expectations. Return of results is increasingly recognized as the new normal. By offering a participant their individual findings, researchers demonstrate respect for participant needs and interests, gratitude for their crucial role in research, and a commitment to minimize risk and to confer benefit whenever possible.

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