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# Return of Genomic Results to Research Participants: The Floor, the Ceiling, and the Choices In Between

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As more research studies incorporate next-generation sequencing (including whole-genome or whole-exome sequencing), investigators and institutional review boards face difficult questions regarding which genomic results to return to research participants and how. An American College of Medical Genetics and Genomics 2013 policy paper suggesting that pathogenic mutations in 56 specified genes should be returned in the clinical setting has raised the question of whether comparable recommendations should be considered in research settings. The Clinical Sequencing Exploratory Research (CSER) Consortium and the Electronic Medical Records and Genomics (eMERGE) Network are multisite research programs that aim to develop practical strategies for addressing questions concerning the return of results in genomic research. CSER and eMERGE committees have identified areas of consensus regarding the return of genomic results to research participants. In most circumstances, if results meet an actionability threshold for return and the research participant has consented to return, genomic results, along with referral for appropriate clinical follow-up, should be offered to participants. However, participants have a right to decline the receipt of genomic results, even when doing so might be viewed as a threat to the participants' health. Research investigators should be prepared to return research results and incidental findings discovered in the course of their research and meeting an actionability threshold, but they have no ethical obligation to actively search for such results. These positions are consistent with the recognition that clinical research is distinct from medical care in both its aims and its guiding moral principles.

## Introduction

The growth of next-generation sequencing and the vast amounts of data that sequencing potentially provides for interpretation require the review of policies for returning results to participants. As the technology and the type of results available continue to evolve, this area requires ongoing scrutiny. An American College of Medical Genetics and Genomics (ACMG) policy paper published in 2013[1] and associated clarification[2] have addressed the return of incidental findings to patients undergoing clinical genomic sequencing tests and have directed attention to whether recommendations of this kind should be considered by the research community. Members of the Return of Results (ROR) committees of the Clinical Sequencing Exploratory Research (CSER) Consortium and the Electronic Medical Records and Genomics (eMERGE) Network, as well as the eMERGE Consent, Education, Regulation, and Consultation (CERC) working group, met to consider this area and worked to identify consensus recommendations. The views expressed in this paper are those of the authors and are not necessarily those of all members of the CSER Consortium or the eMERGE Network, or the NIH.

Only a decade ago, many institutional review boards (IRBs) required a consent form that stipulated to research participants that they would not be given their genetic results. This approach was challenged when the research results could change clinical care.[3] The NHLBI convened a working group that published a 2006 position paper[4] recommending the return of genetic results identified in the course of research to study participants "when the associated risk for the disease is significant; the disease has

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important health implications such as premature death or substantial morbidity or has significant reproductive implications; and proven therapeutic or preventive interventions are available." This concept of clinical utility is often summarized as "actionable" genetic results. The issue of return of genomic results was reviewed in 2010 by a second working group and reported by Fabsitz et al.[5] This group offered further recommendations and emphasized that consent from a research participant is a necessary precondition for returning results. The group struggled with whether research results offered for return must be generated by a laboratory that complies with the Clinical Laboratory Improvement Amendment (CLIA) regulations of 1988[6] in order to be returned, and the group recommended that this question be further evaluated. A 2008 NIH-supported research group offered consensus recommendations reinforcing the need for consent from a research participant in order for incidental findings to be returned and similarly concluded that "more work" was needed for resolving the CLIA issue.[7] This group's recommendations emphasized the difference between research and clinical care and noted that researchers "generally have no obligation to…affirmatively search for" incidental findings. A related NIH-supported research group offered recommendations in 2012 for genomic research involving biobanks, again emphasizing the importance of consent for the return of individual research results and incidental findings and calling for "working with the CMS [Centers for Medicare & Medicaid Services], the agency that administers CLIA" to resolve the question of how to handle results generated in a lab that is not CLIA certified.[8] Finally, the Presidential Commission for the Study of Bioethical Issues has addressed the return of incidental findings in whole-genome sequencing[9] and then more broadly in research.[10] In both reports, they have stressed the importance of seeking the research participant's consent for the return of incidental findings. The latter report concludes that investigators have no duty to affirmatively hunt for such findings and notes the ongoing debate about CLIA's application to the return of findings from laboratories without CLIA certification.

Considerable research has addressed research participants' desires regarding the return of genetic and genomic research results. Data demonstrate that a majority of research participants express interest in receiving clinically significant individual study results.[11,12] Participants consider the potential for treatment and prevention, understanding of a disease, and respect for research participants' right to receive results as compelling reasons for investigators to share research results with participants.[13–15]

As the research community has been grappling with issues around the return of research results and incidental findings, the ACMG published a policy paper[1] addressing the return of incidental findings in clinical settings. The recommendations and ensuing discussion have led the research community to consider the applicability of these or similar recommendations in research contexts. The ACMG recommendations urge that laboratories evaluate and return known pathogenic and expected pathogenic variants in 56 genes when those data are available through clinical next-generation sequencing tests, including whole-genome or whole-exome sequencing performed for diagnostic or treatment purposes for any indication, including when germline testing is done as part of a tumor-normal pair in oncology. The ACMG clinical recommendations have generated much controversy.[16–21] However, little of the controversy revolves around the actual list of minimum genes suggested, although larger lists have been offered, including those from members of the CSER Consortium.[22] Rather, the controversy has been focused on two issues. One issue is the recommendation of mandatory analysis and return of results, even if the patient does not desire such information; it has been argued that this might be inconsistent with established norms of respect for patient autonomy[20,23] and might pose liability risks that need to be managed carefully.[21] Notably, the ACMG has recently abandoned the mandatory position in favor of a patient opt-out of the analysis and return of incidental findings.[24] The second major area of controversy centers on the return of pathogenic variants for adult-onset conditions to children.[25] Nonetheless, the specific question of whether these or comparable recommendations should be extended to research genomic tests has been frequently raised. This debate underscores the need for an updated consideration of which genomic content should be evaluated and which results should be returned in the research setting.

## Material and Methods

### Process

A joint meeting of the CSER Consortium and eMERGE Network in October 2013 included the ROR committees of both groups. This meeting identified the return of genomic results to research participants as an area of joint concern. Those attending agreed on some basic principles to inform the return of research results, including incidental findings. A written proposal to produce a paper summarizing these basic principles was shared with both consortia, and all members were invited to join the process. Whereas the CSER Consortium Actionability (Act)-ROR group encompasses a large bioethics presence, the eMERGE bioethics group is spread between the ROR and CERC working groups; thus, the latter group was formally invited to join the process. A small writing team wrote a first draft based on the October discussion and then shared it with co-authors for primary input. That product was then reviewed by the working groups, whose feedback was incorporated in an iterative process of revision.

### Guiding Principles

Principle 1: Research, even in a clinical setting, differs from clinical care in both its goals and its procedures; as a result, the minimal and maximal information returned in a research setting might differ from standards of clinical practice.

Principle 2: Resources for research should be primarily directed at scientific discovery; thus, researchers do not have a duty to look for actionable genomic findings beyond those uncovered in the normal process of their investigations.

Principle 3: Research assessing the outcomes of a wide range of potential practices for returning genomic results is required for the ultimate formulation of best practices in both the research and the clinical settings.

Principle 4: Analytically and clinically valid information that is of an important and actionable medical nature and that is identified as part of the research process should be offered to a research participant.

Principle 5: Participants should have the right to refuse any results that are offered. Potential research participants or parents of minors eligible for research studies should be provided proper informed consent that respects autonomy, including the right to refuse participation in research. If the return of results is essential to the purpose of the study, potential participants should be adequately informed at the time of recruitment so they are able to decline participation if they do not want to receive results and should be reminded of their right to withdraw prior to any return of results.

## Results and Discussion

### Areas of Consensus

*Principle 1*

"Research, even in a clinical setting, differs from clinical care in both its goals and its procedures; as a result, the minimal and maximal information returned in a research setting might differ from standards of clinical practice." This principle acknowledges that standards for return practices in the research setting should not be driven purely by clinical standards. The distinction between research, an activity focused on the acquisition of generalizable knowledge, and clinical care, an activity focused on the treatment and decision making for the patient, is important in determining an appropriate practice for the return of genomic research results.[21,26] Despite the frequent attestations that genome-scale sequencing is "blurring the lines between research and clinical practice," these endeavors have distinct goals and characteristics. The relationship between the physician and the patient differs from the relationship between the researcher and the research participant and incorporates the legal responsibilities of patient care on the part of the clinician. That said, researchers should acknowledge certain important ethical obligations toward participants, including respect for persons, a duty to avoid harm, and a duty to rescue[27] in defined circumstances.

*Principle 2*

"Resources for research should be primarily directed at scientific discovery; thus, researchers do not have a duty to look for actionable genomic findings beyond those uncovered in the normal process of their investigations." This principle acknowledges that the return of genomic research results represents an investment of limited research resources and that returnable results are found in a small proportion of participants.[28] We therefore do not endorse the requirement to search for "incidental findings," such as that proposed in the ACMG 2013 recommendations, in the research context. Although the ACMG recommends a hunt for incidental findings in a predetermined list of genes whenever relevant clinical sequencing is undertaken, the term "incidental" is somewhat of a misnomer and has been propagated by the common misconception that identifying such results is unavoidable. Although most routine variant-calling algorithms capture all genetic variants (if present) across the entire genome, most study designs do not require these data to be evaluated, and thus the presence or absence of a meaningful genetic variant is usually unknown to the investigator unless a purposeful examination of a particular gene is undertaken. Further, even if these data are generated and evaluated, confirming that a purported disease-causing variant is actually pathogenic often requires extensive review, including evaluation of the primary literature. Even in a highly automated study reported by Dorschner et al., which included most of the genes proposed by the ACMG, among others, this work required an average of 20 min of review per variant (the majority of which were nonpathogenic), and some variants required hours of review and discussion.[28] Issues also arise in the return of such results. Further resources must be utilized for providing confirmation in a CLIA-compliant lab (if required) and for returning the result. Additionally, some investigative teams are not qualified to interpret and/or return the results. Thus, although it is true that in a large study some participants might have their health protected by the search for and the return of genomic "incidental findings," such activities require expertise and substantial investment in resources. Notably, the recent Presidential Commission for the Study of Bioethical Issues considering incidental findings has also concluded that researchers do not have a "duty to hunt."[10]

It would be exceptional to mandate the use of research funds to hunt for "incidental findings," in effect a low-yield preventive health screening of participants; if this were recommended, one could think of many interventions that would most likely yield a higher benefit. In addition, as discussed earlier, research is separate from the provision of medical care and screening; researchers are not obligated to develop expertise and expend additional resources to look for variants to return. Rather, we favor defining the "floor" for the offer of the return of genomic results in research studies to include highly actionable findings that are relevant to the intent of the research study or that are "stumbled upon" in the course of research. Relevant costs to a study could be estimated and included in the budget, and granting agencies should allow these costs. Any obligation to return results would not extend beyond the funding period. Similarly, it would be unreasonable to expect all researchers engaged in genomic research to provide their research participants with broad access to genomic results if doing so in a

responsible way represented an unreasonable burden that distracted from the intent and purpose of their research studies.

*Principle 3*

One of the broad goals of genomic research, and a specific goal of the CSER Consortium and eMERGE Network, is to better understand the optimal return of results. In order to do this, one should explore a variety of methods. This leads to principle 3, "research assessing the outcomes of a wide range of potential practices for returning genomic results is required for the ultimate formulation of best practices in both the research and the clinical settings."

We recognize a range of possible results that could be returned in a research setting; we define the minimal "floor" as the return of well-established, important actionable genetic findings relevant to the intent of the research study or uncovered in the course of usual research procedures, and we define the "ceiling" as the entire genome sequence or some representation of it. Thus, for the return of results in a research setting, the "floor" would be lower than the clinical return policy of the ACMG recommendations, and the "ceiling" of acceptable return (including of the entire genome) would be higher for at least the near future. Findings from CSER, eMERGE, and other research studies investigating a wide range of practices for the return of genomic results will help inform current and future policies for both research and clinical return-of-results recommendations in this area.

As genomic medicine becomes more common, we can anticipate that patients might be given direct access to the entirety of their genomic information. This warrants research that delves into optimal procedures for doing this, including pretest counseling, informed consent, posttest understanding, avoidance of misinterpretation, health-care and personal utility, and cost evaluation. Therefore, researchers might elect to return all genomic information. Research into these and related questions might be best designed to return a variety of information between these extremes. For example, research on the effects of variants on medication prescribing and compliance might only require the return of pharmacogenomic data.

*Principle 4*

Endorsed by Bookman et al.,[4] Fabsitz et al.,[5] and others, we recognize that when investigators have a valid research result that will allow preventive or other steps important to protect the participant's health, these data should be offered to identifiable research participants. This is supported by the fourth principle that "analytically and clinically valid information that is of an important and actionable medical nature and that is identified as part of the research process should be offered to a research participant." This assumes that the participant has consented to the return of results in the informed-consent process. The definition of what is actionable is a matter of judgment. The gene-disease pairs offered by the ACMG might be a reasonable starting place for consideration, although there are clearly other equally actionable, if rarer, examples.[28] Further, what is appropriate for return might depend on context,[27] such as the age of the participant. What is considered returnable should be examined by the investigators and outlined in the consent process. We also support the Fabsitz et al. position that the investigators' responsibility to return does not extend beyond the period of funding, although investigators might elect to return results beyond that timeframe. We also suggest that secondary users of data return information to the primary investigators but are not themselves obligated to return results to participants. We acknowledge that some studies, including those of anonymized participants, will not be able to return results.

There has been controversy over whether adult-onset findings should be offered for pediatric research participants. Historically, children have not been offered elective clinical testing for adult-onset conditions. This preserves their autonomy to make their own decisions regarding testing when they are adults. However, we acknowledge that the case of an incidental finding discovered in sequencing DNA from a child with no prior warning of that variant in the family is different from the past clinical case of the known existence of the genetic finding in one or more other family members. When a family member is known to carry a pathogenic variant for a highly penetrant adult-onset condition for which there is no change in childhood management (such as screening tests or diet), there is little possible benefit to the child or family from testing for this variant during childhood. This is reflected in the traditional medical genetics practice guidelines that children not be tested for adult-onset conditions that are known in their family.[29–31] However, when the variant is unknown in the family and a pediatric genomic test uncovers it as an incidental finding, return alerts family members to be tested for it. The ACMG[1] authors, in concluding that these results should be returned in the clinical setting, regarded the prevention of potential harm to the transmitting parent and other family members as a benefit to the child. By contrast, the P3G international pediatrics platform group recently recommended that "mutations that predispose the child to develop an adult-onset disorder, even if accidentally discovered in the research process, generally should not be returned. This allows the child to make his or her own decision about receiving the results as an adult." [32] They also added that "questions, which should arise rarely, of whether the child would benefit, on balance, from disclosure because of the potential benefit to the family from knowing about a highly penetrant gene they may have that poses serious risk to health and that is preventable or treatable, should be assessed on a case-by-case basis."

This topic calls for further research and analysis. When an incidental result found in a pediatric research study is not returned, current practice makes it unlikely that the result will be offered to the child in adulthood because,

unlike a known familial mutation, its existence is not likely to be tracked. Further, the frequency or rarity of incidentally discovered mutations whose known existence might benefit the family warrants research, given that 1%–4% of participants might have such variants.[28] In the case of a pediatric research participant, we are able to reach consensus and conclude that during the consent process, the parents should be offered the choice of whether to have the adult-onset actionable incidental findings returned along with counseling on the implications for the child's best interests and the parents' health status. One caveat to this approach is that in the case of trio sequencing, where the parents and child are all sequenced, adult-onset actionable findings that do not change management during childhood and are detected in a parent need not be offered for return to the child.

*Principle 5*

This principle states that "participants should have the right to refuse any results that are offered. Potential research participants or parents of minors eligible for research studies should be provided proper informed consent that respects autonomy, including the right to refuse participation in research. If the return of results is essential to the purpose of the study, potential participants should be adequately informed at the time of recruitment so they are able to decline participation if they do not want to receive results and are reminded of their right to withdraw prior to any return of results."

At the time of consenting, participants should be given the opportunity to refuse the return of genetic findings, unless the purpose of the study is dependent on result return, in which case consent to participate in the study necessarily involves consent to receive results. In the latter case, participants may decline enrollment.

Studies suggest that research participants vary in their desire for genomic results. Many research participants would like more than highly actionable data, including data on nonactionable findings.[33,34] This is born out in the market for direct-to-consumer testing, suggesting interest by some for information about minimally actionable conditions, ancestry information, and carrier status for recessive diseases. On the other hand, a substantial number of participants indicate that they want no genomic information or assign no monetary value to having this information.[35] Research on these varying levels of return, ranging from the "floor" to the "ceiling," will not always honor participant preferences. It is ethical to not share genomic information that some participants might want as long as they have a clear understanding of the limits when they enroll in the study. The converse might not always be true, however. It might not be ethical to return results that participants do not want if they feel compelled to be in a study for possible medical gain. For example, patients undergoing research-based tumor sequencing for possible direction of chemotherapy should be able to decline the return of incidental findings not related to their cancer treatment. Participation in research studies should be as noncoercive and respectful of participant choice as possible.

The consent process and form should address the possibility that there might be both research results related to the primary intent of the research and findings that are incidentally discovered in the course of research, and participants should be able to clearly opt in or out of receiving these types of results either at the time of initial consent or at a later point in the study when the specific types of results the participants might receive can be best defined. Framing the conversation as "if we find…would you want" avoids the potentially coercive "we have…do you want." Ideally, the original consent form would include the possibility for, or an option of, future contact to offer results not anticipated at the time of consenting. If, as a result of the study design, it is not possible to refuse genetic research findings, this should be clearly outlined and consented to in the informed-consent process. Participant preferences might play a role in the choice of which research results should be returned in that all participants might not choose the same options as those deemed clinically significant. Research is warranted for how to best educate participants on their options and possibly offer more choices on types of results for return. Although we do not anticipate a scenario in which an opt-out of genomic findings or future contact would be overruled by the study team, we do envision a role for the local IRB or data- and safety-monitoring board as to whether the opt-out might be overruled if unexpected and clinically urgent circumstances arise.

We suggest that, when feasible, participants be reminded of their right to refuse genomic results prior to receiving them. Circumstances that lead participants to change their minds are another important area for research. We do not believe written reconsent is required prior to the return of results.

Parents too should be able to refuse the return of results and incidental findings when their children participate in genomic research. This latitude to refuse may be limited, however, when the results hold high and actionable health significance for the minor during childhood. This is in keeping with the broad discretion generally accorded to parents to make health decisions in their child's best interests, except regarding conditions that threaten life or significant impairment.[36–38]

## Areas of Controversy

Our group has two remaining areas of controversy in the return of research results: (1) the role of CLIA compliance and (2) the optimal methods for return. Each of these areas would benefit from additional research. In the first area, Fabsitz et al.[5] did not reach consensus on whether results returned to participants must be CLIA compliant. We agree that results whose accuracy or sample origin is in question should not be returned without compelling

reasons and careful explanation. There is also general agreement that prospective studies that include a plan to return genetic results should derive or confirm those results in CLIA-compliant labs when possible. However, actionable information might be learned from assays that cannot be easily confirmed in a CLIA-compliant laboratory. In addition, even if the result can be confirmed, the existing samples might not have been obtained and stored through a CLIA-compliant sample-tracking process, and a new specimen must also be obtained for ensuring that no sample mix-up occurred. One option is to disclose the non-CLIA-compliant results as research results with the caution that no clinical action should be taken on the basis of those results while providing information about how to proceed with clinical confirmation in a process of clinical evaluation and follow-up. This clinical confirmation might require a genetics professional, given that primary-care providers might not have the expertise to order a confirmatory test and perform counseling. Some have suggested that the return of the non-CLIA result and subsequent referral to appropriate care for a CLIA test, if desired, not be allowed under the CLIA regulations; however, the only published legal analysis concludes that this approach is within the CLIA research exception and therefore does not trigger the need for CLIA compliance.[26,39] This analysis also concludes that there is a First Amendment right for a willing researcher to share non-CLIA results with a willing participant,[39] although this interpretation has not been tested in court. Given that research circumstances might make a CLIA-compliant test impossible, research into whether there is harm or benefit to sharing non-CLIA results might be helpful.

The second area of controversy, the method of return, also requires further research. Results should be communicated effectively and presented in a way that is understood by the participant and their health-care provider. Research is under way on how best to integrate genomic findings into the medical record and which alerts or decision-support prompts would aid the provider. The clinician is then responsible for integrating the results into a clinical-care plan as appropriate in consultation with the patient. Access to follow-up clinical care should be available. Optimal methods for communicating genomic results will vary with context and will ideally maintain a clear boundary between clinical care and research. Some have proposed that genetic research results only be returned by a genetic counselor or other qualified clinical provider. Others have investigated other methods for return, such as by the primary-care provider or through computer-aided or web-based return.[40,41]These latter models are driven by the expectation that genomic results will become more common and that their return will require nongenetics professionals, given how few clinical geneticists and genetic counselors are available. Again, research comparing methods of results return could help identify best practices.

**Consensus Recommendations**

1. At a minimum (the "floor"), researchers should offer individual genomic research results that are valid, medically important, and actionable if discovered purposefully or by chance during the course of data analysis. Investigators are not obligated to search for actionable genomic variants to be returned beyond those identified in the course of their research, that is, there is no duty to hunt.
   a. Given that there is no definitive "list" of medically actionable findings with respect to the return of research results and incidental findings and that such a list would be context dependent, those involved in genomics research should give thought to the types of findings that would represent the "floor" for return in their study in consultation with local IRBs and funding agencies. The ACMG list, currently containing 56 genes, is a reasonable starting point for consideration;[1] however, more comprehensive lists have been offered.[22]
   b. The responsibility to offer disclosure of results and incidental findings is limited to circumstances in which there are identifiable participants and to the period of funding to investigators, although investigators may elect to offer disclosure after that term.
2. Participants should have the option to refuse research genomic test results, both those related to the study purpose and those that are incidental findings, unless the study aims are related to the return of these data. Plans for return and the participants' option to refuse offered results should be addressed at the time of consent.
   a. When studies do not allow participants to opt out of potentially receiving results, this and the opportunity to withdraw prior to receiving results should be clearly addressed in the consent process and form.
   b. The consent process and form should clarify the circumstances in which a participant might be contacted in the future and explicitly ask whether the participant consents to future contact if new findings are found. Participants who are contacted regarding such results should have the right to decline receiving those results.
   c. Participation in research studies should be noncoercive and respectful of participant choice.
   d. Parents of minors participating in genomic research should generally have the same right to refuse, unless the return of the results is of high health significance to the minor in childhood. Investigators may reasonably offer the parents of minors participating in pediatric research the option of accepting or refusing results for adult-onset conditions along with

counseling on the implications for the child's best interests and the parents' health status. In the case of trio testing, parents may be offered only their own adult-onset results and not their child's, unless the child has a relevant de novo mutation.

3. Researchers might be ethically and scientifically justified in returning all genomic information (the "ceiling") in some format and any level of information in between the "floor" of actionable results identified during the course of research and the "ceiling" of all genomic information.
   a. Special care should be taken when the benefits and harms of returning a particular type of genomic information are uncertain.
   b. Investigators should take steps to assure adequate analytic and clinical validity for return, including systems to avoid sample mix-up. Further work is needed on the role of CLIA compliance in the return of research results.
   c. Research studies intended to examine practices for the return of genomic information should include measurements of benefits and harms in the design of the study.
4. Additional research projects that examine the potential benefits and harms of receiving genomic results and evaluate practices for returning genomic information are required to inform the increasing use of genomic sequencing in clinical research.

## Consortia

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