

Opportunities and Implications for Research Stemming from the ACMG Recommendations for the Return of Incidental Findings in Clinical Genome Sequencing

February 18-19, 2014
Rockville, MD
Workshop Summary

Overview

On February 18 and 19, 2014, the National Human Genome Research Institute (NHGRI) convened experts to discuss the potential implications on research policies of recommendations and guidelines regarding the management of incidental findings when patients undergo clinical exome or genome sequencing. The objectives of the workshop were:

- 1) To discuss key questions and challenges in determining the role (if any) of clinical recommendations in shaping research policies (using the recent American College of Medical Genetics and Genomics (ACMG) recommendations as a point of departure), and
- 2) To inform NHGRI about what the Institute should consider in developing a normative and scientific research agenda and a policy agenda relating to the return of incidental findings in clinical and research settings.

Workshop attendees represented academia, government, health care professionals, institutional review boards, the Presidential Commission for the Study of Bioethical Issues, professional societies, and the UK Biobank. Please see the workshop agenda and attendee roster for more information.

Summary of Presentations

Overview, Context, and Next Steps for ACMG Recommendations

Speaker: James P. Evans, M.D., Ph.D.

There is a perceived need for clinical sequencing guidelines as large amounts of data are being generated, including data unrelated to the clinical indication for which the test was ordered, without any standards to guide analysis and reporting. The ACMG recommendations are the expert opinion of an ad hoc group of medical geneticists, and they are intended to be a starting point for discussion rather than a final statement. They leave many implementation questions unanswered (such as defining who should report findings and by whom the data should be filtered), and the selection of genes to include is limited by insufficient evidence, especially for penetrance in unselected populations. In addition, the recommendations provide bounds for clinicians' "duty to hunt," but they do not include a role for patient choice. To move forward, the community needs to define the essential elements of such guidance and determine where compromises can be made (e.g., allow opt-out option for patients). Guidelines for research should reflect the context within which the genome sequence is generated (i.e., research vs. clinical care), satisfy the core principles that make research ethical (i.e., beneficence, autonomy, justice), and balance the potential harms of over- and under-reporting.

Given the need to balance return of incidental findings with the research context, a list of genes, like that published by ACMG, may be too constraining. A potentially more feasible approach is to define a floor and ceiling for return of anticipatable incidental findings — researchers would be expected to return a minimum set of results if found, and could decide to offer additional results depending on patient preferences and resources. Subjects could be allowed to opt out of receiving almost all results, with the

provision that investigators could re-contact participants to offer findings in exceptional circumstances when a high bar is met.

Professional Society Perspectives

Speakers: Elaine Lyon, Ph.D., Joseph D. McInerney, M.A., M.S., and Kelly Ormond, M.S., C.G.C., L.G.C.

Dr. Lyon, Mr. McInerney, and Ms. Ormond provided professional society perspectives, representing the Association for Molecular Pathology (AMP), American Society of Human Genetics (ASHG), and National Society of Genetic Counselors (NSGC), respectively. All three groups have active roles in the discussions regarding the management of incidental findings. ASHG and AMP plan to develop their own recommendations regarding management of incidental finding. NSGC is interested in participating in the discussions regarding management of incidental findings, as their members are taking a primary role in informed consent and return of results.

Collaboration within and between professional societies is necessary to navigate the issues involved in management of incidental findings. Questions and issues that must be addressed in order to implement return of results in the clinical and research contexts include:

- Collecting more data on ascertainment bias issues to be able to accurately assess risk,
- Identifying any variables that could predict who would decline testing if return of certain incidental findings was obligatory,
- Short and long-term psychosocial responses to return of results, and
- Whether an opt-in or opt-out model for return of incidental findings should be pursued.

During the discussion, attendees debated whether or not genetic information is “exceptional” and should be managed differently than other clinical information. They discussed the need for more evidence to show the utility of genetic tests and the need for data on how people respond to receiving results. In addition to guidelines on what information should be returned, workshop participants noted the need for guidelines on how to return results.

Lessons Learned from Other Fields

Speaker: R. Nick Bryan, M.D., Ph.D.

Dr. Bryan discussed the management of incidental findings in radiology. The prevalence of incidental findings generated through imaging analyses varies greatly. Incidental findings increase with patient age, and they vary depending on the location of the imaging and the imaging technology. Radiologists have little interest in guidelines for “managing” incidental findings—all information of potential clinical importance is reported to patients. The “right not to know” has not been a prominent consideration in radiology. There is no “duty to hunt” beyond what is required for the clinical indication or research study. For some clinical indications, only part of the image is analyzed (the section relevant to the clinical indication), which can be problematic in the event of litigation if a potential incidental finding is missed; common guidance is to order the narrowest test suitable to establishing a diagnosis.

In the discussion following the presentation, it was noted that most radiological information is diagnostic and little is predictive, while a higher proportion of genomic information is predictive rather than diagnostic.

Research Questions Related to Normative Issues When Moving from Research to Clinical Care

Speakers: Jeremy Garrett, Ph.D., Christine Grady, M.S.N., Ph.D., and Scott Kim, M.D., Ph.D.
Moderator: Benjamin Berkman, J.D., M.P.H.

The speakers discussed reasons for and against incorporating clinical recommendations/guidelines into the research context. There are four elements to consider when determining if guidelines should be adopted in research: the purpose of the guidelines, the evidence base for the guidelines, the process used to generate the guidelines, and the adoption of the guidelines by the community. If guidelines are high quality and accepted in the clinical community, the research community may need to justify deviating from them. Justifications could include the differences between the purposes of research and clinical care, differences between the clinical and research populations (i.e., patients versus subjects), differences in clinician and researcher obligations, and feasibility of following the guidelines (e.g., secondary researchers returning incidental findings on de-identified data/specimens). It was argued that because of these differences, nondisclosure of incidental findings to research participants may be justifiable.

However, some distinctions between clinical care and research are significant while some are insignificant, so it can be problematic if there are different guidelines for the two settings. “Actionability” has been suggested as a threshold for return of incidental findings, but actions that a clinician can pursue may be different from the actions that a researcher or research participant can pursue, particularly if the subject has limited access to health care. The speakers questioned whether there are conditions that are universally actionable. They also questioned whether it is appropriate to prohibit research participants from opting out of receiving incidental findings.

Incidental Findings in Exome/Genome Sequencing

Speaker: Robert Nussbaum, M.D.

Dr. Nussbaum discussed whether management of incidental findings in exome/genome sequencing is a novel paradigm, or if there are parallels and pre-existing paradigms in clinical medicine. A significant problem in both clinical care and research is difficulty in determining what variants mean. To interpret variants, robust databases with patient variants and phenotypes are needed, which could be created by turning the molecular genetic testing industry into a learning healthcare system.

One approach to managing incidental findings in research is to require that participants have clinicians to whom results can be returned. However, this approach can lead to biased ascertainment by excluding potential participants who do not have primary care providers. Participants discussed whether it is appropriate to state in the informed consent that no individual incidental findings will be returned. They generally agreed that it is acceptable in some circumstances, but it was noted that such statements could be problematic by preventing communication of unforeseen, highly actionable incidental findings. If the informed consent form allows re-contact, it should not set up the expectation that no re-contact indicates that nothing of concern was found for the participant.

Participant and Participant Protection Perspectives

Speakers: Benjamin Berkman, J.D., M.P.H., Jeffrey R. Botkin, M.D., M.P.H., and Wendy Chung, M.D., Ph.D.
Moderator: Laura Lyman Rodriguez, Ph.D.

The speakers discussed the problems that IRBs face related to return of incidental findings. IRBs are not experienced with the issues involved in return of incidental findings, and neither federal regulations nor

the Office for Human Research Protections (OHRP) provide guidance. It is not the role of the IRB to determine what results should be disclosed, but it is appropriate for IRBs to expect investigators to address incidental findings in their protocols and to set general institutional standards relating to such. The Clinical Laboratory Improvement Amendments (CLIA) regulations require that individual results returned to participants for the diagnosis, prevention, or treatment of disease, or for the assessment of the participant's health must be generated in CLIA-certified laboratories. CLIA is intended to ensure the quality of clinical laboratory testing, but the requirement to generate or confirm results in a CLIA-certified laboratory can impede the return of incidental findings.

Dr. Berkman provided data from a survey of IRB member views on incidental findings. IRB members endorse the "right not to know" as a general principle, but this endorsement drops when respondents were presented with a concrete case. Autonomy, beneficence, and the "duty to warn" are reasons why respondents believe that it is important to return incidental findings. Inadequate clinical or analytic validity and inadequately demonstrated clinical utility were cited as reasons to not return incidental findings. Lack of time and resources did not have significant support as reasons not to return incidental findings.

The speakers also explored the topic of participant preferences regarding return of individual results. In one project, participant preferences were requested before and after a pre-test counseling session, and participants were asked for feedback during a post-test debrief session and follow-up sessions at various intervals. Most participants wanted to receive some types of individual results. Participants' interest in receiving results varied by race, age, and other factors. Most participants had a positive reaction to the research.

Research Questions Related to Medical Analysis of Genomic Data when Moving from Research to Clinical Care

Speakers: Leslie Biesecker, M.D. and Heidi L. Rehm, Ph.D., F.A.C.M.G.

Moderator: James P. Evans, M.D., Ph.D.

The speakers stated that the field has moved beyond hypothetical situations, and there is a growing experience base describing what patients do when they receive results. Research is needed on the frequency of and reasons for patients opting out of receiving results. Data relating to both emerging experience and additional research questions would inform decisions about setting relevant thresholds for returning incidental finding when identified. In order to improve our understanding of variant function and clinical utility, another fundamental point of information in setting expectations for returning incidental findings, clear evidence standards and more data sharing are needed. Data from clinical laboratories are largely absent from the public domain, and research findings generally lack standardized interpretations or assertions. Quantitative metrics of utility/actionability are needed, and outcomes data should be collected. The validity of gene- and variant-disease associations should be evaluated and improved.

Disagreement about how to manage genomic incidental findings could in part be due to how the issues are framed. Predictive medicine and incidental findings provide similar information, but the term "incidental findings" induces greater controversy. Similarly, the idea of genetic exceptionalism calls attention to the issues in genomic medicine and research and impedes genomics from diffusing into other healthcare fields.

In the discussion following the presentations, a research agenda was suggested:

1. Define clinical utility standards to inform the establishment of the minimum (“floor”) and maximum (“ceiling”) set of anticipatable incidental findings to return
2. Determine how to bin variants or findings under these standards
3. Improve the understanding of variant penetrance in asymptomatic/unselected populations
4. Educate researchers and clinicians
5. Develop evidence to allow for better measurement of outcomes and to help facilitate evaluation of the impact decisions based on genetic information are having on health

Research Questions Related to Participant Perspectives and the Ethics Issues when Moving from Research to Clinical Care

Speakers: Barbara Bernhardt, M.S., C.G.C. and Laura M. Beskow, M.P.H., Ph.D.

Moderator: Gail Henderson, Ph.D.

There are a number of ethical, legal, and social implications (ELSI) issues that relate to the generation of recommendations for managing incidental findings. In addition, the development and implementation of standards for managing incidental findings provides an opportunity to study the standards process as it happens.

Ms. Bernhardt discussed what is being learned through the Clinical Sequencing and Exploratory Research (CSER) Program. The program is designed to explore the generation and use of genomic information in clinical care. The nine funded projects examine different populations and include analyses related to returning genome sequence results. Issues being studied include the context in which patients consider incidental genomic findings, how participants feel about sharing data, types of incidental findings to return, and how to improve the informed consent process for whole genome sequencing in the research context. There is also research being performed on managing genetic findings for children. Researchers are learning how to facilitate the participation of children in the discussion and will collect data on the outcomes of offering predictive information to children.

Dr. Beskow noted that research falls along a continuum (from basic science involving samples from a researcher’s institution, to biobanks, to case-control studies, to randomized control trials, to sequencing to find a genetic diagnosis). Research is not homogenous, so a one-size-fits-all policy for managing incidental findings across the continuum may not be feasible or appropriate. Guidelines should recognize that there are different research contexts, and the clinical context is yet another realm.

During the discussion, agreement developed around the point that in developing a research agenda, it is important to consider what kinds of research programs are useful in evaluating how patients and participants understand incidental findings (perhaps differently) and what impact the findings have in their lives. While the ACMG recommendations are a new standard and clinical laboratories should thoughtfully consider following them, as with any standard of care, research should be performed to test and improve upon this first edition.

Implementation Issues to Consider

Speakers: Robert C. Green, M.D., M.P.H., Katie Lewis, M.S., C.G.C., and Jonathan Sellors

Moderator: P. Pearl O’Rourke, M.D.

There are a variety of issues that must be considered when implementing guidelines for managing incidental findings in research involving genome sequencing. The speakers noted that there are many challenges related to research participants. In her research, Ms. Lewis finds that participants are very interested in receiving their results. Participants want to feel that they have control over their data. They

want to be able to talk with qualified professionals about the meaning of their results and leave with options for responding to the information. They appreciate assistance in connecting with healthcare providers and advice for informing their family members.

While autonomy is important to participants, researchers must consider a number of other factors in managing participant results. Participants sometimes expect more information than researchers plan to provide, and they sometimes interpret a lack of results reported back to them as a negative finding. Some participants do not have a framework to interpret and respond to results. Dr. O'Rourke noted that confusion about clinical care versus research is common and that, in general, there are low levels of scientific literacy and numeracy in the general American population. While information about return of results should be included in informed consent forms, these documents can be lengthy and are often not read carefully, understood, or remembered.

Mr. Sellors provided an overview of the UK Biobank. The Biobank collects samples and data and is in the process of genotyping 500,000 samples. Incidental findings from future assays (conducted after the sample has been donated and the participant is no longer actively engaged in the research) are not returned to the participant. For research scenarios with ongoing patient engagement, the UK Biobank is developing specific protocols for assessing incidental findings that may be returned to participants and the mechanism by which this will be done. Mr. Sellors noted that, as in the United States, duty of care in the United Kingdom is context-based.

Dr. Robert Green observed that society is moving toward an independent, self-motivated approach to health information in embracing personalized, predictive medicine. Based on research data that he and others have generated, participants who are "information seekers" generally react rationally to results. Diagnostic misconception is a real problem, and there should be additional efforts to distinguish research from clinical care.

Factors to Consider in Determining How, if at All, Genomic Research Projects Should Respond to the ACMG Recommendations

Speakers: Benjamin Berkman, J.D., M.P.H. and Karen Rothenberg, J.D.

Based on the discussions during the workshop, Mr. Berkman discussed normative questions about the relevance of clinical guidance to the research enterprise. The baseline question is: when should clinical recommendations or guidelines be adopted by the research community? First, the nature of the guidance should be analyzed. If the guidance is of high quality and widely accepted by clinicians, researchers could need to justify deviance from the guidance.

- What arguments constitute reasonable justification for deviance from clinical guidance in the research context?
- Once the time is ripe for adoption of clinical guidance in the research realm, should they apply universally across all types of research?
- What implications do other factors including the researcher's relationship with subject, researcher's expertise, researcher resources (e.g., genetic counselors), feasibility of re-contact, information generated, and alternate access to important medical information have?

There is no one-size-fits-all approach, but justice and consistency across research contexts are important considerations.

The duty to look for incidental findings was discussed at various points during the workshop.

- Do researchers have an obligation to actively search for at least a limited list of high value variants?
- Is it appropriate to intentionally blind oneself to specified genomic data that has already been generated?
- To what extent should finite research resources be allocated towards supporting the infrastructure necessary to properly return secondary findings?
- Do the contours of the obligation to disclose (and perhaps hunt) shift once we have “push-button” analytic capacity or once genomic medicine is more widely available in the context of general medical care?

Workshop participants discussed and debated the right not to know.

- Is there an absolute right not to know genetic information about oneself?
- What are the benefits and drawbacks of an opt-out paradigm?
- What is the normative basis for a duty to disclose?
- Where are the loci of control (laboratories, clinicians, patients)?
- Does the context (i.e., clinical vs. research) in which the sequencing is performed matter?
- How should pediatric testing for adult-onset disorders be handled?

Workshop participants reported that their research showed that the majority of research participants want to receive their results.

- What, if any, should the role of participant/patient preferences play in a protocol-level decision about managing incidental findings?
- How should preferences that might change over time be assessed?

Some workshop participants suggested that research and clinical care should be distinguished more deliberately.

- Given the traditionally clear distinctions between research and clinical care, what are the potential effects resulting from a blurring of the line between the two settings?
- Where is the distinction helpful and where is it problematic?
- Does the distinction matter to patients in an ethically relevant way?
- Does it matter in both directions?

Informed consent is seen as a good vehicle for helping to manage expectations about what will be returned, but there was acknowledgement by the group that informed consent is just part of an ongoing conversation between the participant and investigator.

- How can informed consent best convey complex genomic information?
- Is it ever appropriate to permanently close the door on returning incidental findings?
- How should the role of the subject’s family be handled?

Workshop participants suggested that the term “incidental findings” is minimizing and not appropriate. If an alternate term should be adopted, what should it be? Finally, a recurring question throughout the workshop was whether genetics is exceptional.

Synthesizing Research Needs and Opportunities

Speaker: Teri Manolio, M.D., Ph.D.

Dr. Manolio summarized and synthesized the research needs discussed during the workshop. Lack of evidence on return of incidental findings, especially impact on patient outcomes, is a key problem. A number of key points were identified:

- Without insurance reimbursement to pay for tests during ongoing clinical research, it will be difficult to generate the needed evidence to establish clinical utility. Different standards may need to be explored for rare variants, as the community may never have enough evidence.
- The strength of evidence for gene-disease associations, variant pathogenicity (penetrance, including in unselected and diverse ancestry patients), and utility (medical, economic, personal) must be strengthened.
- The community should apply the full range of epidemiologic study designs to actionability, from biobanks to clinical trials, and should define what can be learned from each of these types of research designs.
- The community should define relevant outcomes, such as disease incidence, morbidity, mortality, and adverse events.
- Low frequency risk variants and outcomes should be investigated, but barriers include the large numbers of patients and long follow-up time required for such investigations.
- The community needs to consider how to manage variant carriers from families with weak family history due to small family size or variants of lower penetrance.
- The community needs to define which non-loss-of-function variants are likely pathogenic. Informatics solutions (e.g., “push-button” analytic capacity) are needed. Better biologic systems to assess function are also needed. The community should consider how to collapse variants for association analysis and examine mechanisms for reinterpretation.

There are many issues related to research participants to be addressed:

- The research community needs to identify metrics to guide the development of policies for returning results and incidental findings, as personal utility is too vague and variable.
- The appropriateness of limiting the amount of data generated should be explored as a possible approach for minimizing concerns about incidental findings.
- The best approaches for obtaining informed consent and addressing the right not-to-know should be identified. Data should be collected about how often and why patients opt out of receiving information about themselves.
- The research community needs to explore how best to manage subject and patient expectations.
- An option for “locking up” children’s results and reporting them when the children are ready should be explored.
- Research should be performed to explore the appropriate role of family preference in testing the proband?
- The community should look into new ways for family members to share genetic and clinical information. Even when studying the clinical end of the spectrum, investigators should study how patients understand these findings and what impact they have on their lives.
- Researchers should share and use validated measures across studies.
- Researchers should study the relationship between motivations to participate in research and the reaction to the information returned.

Research is needed related to implementation of guidelines include defining educational needs, the most effective educational approaches, and on the validity and robustness of standards. The community also needs to identify what information should go into the electronic health record (EHR) and the level of alert that should be assigned to it.

Synthesizing Policy Needs and Issues to Develop

Speaker: Laura Lyman Rodriguez, Ph.D.

Dr. Rodriguez summarized and synthesized the policy needs discussed during the workshop. First, better definitions are needed:

- The community needs consistent and clear terminology for incidental findings and for how/if the current challenge is different.
- The community needs to define the roles and obligations for each scenario and relationships (biobank, clinician, IRB, laboratory, participant, patient, researcher).

The development and implementation of guidelines involves other policy needs:

- A methodology to consider questions and determine what is imperative for the field is needed.
- The community needs to establish criteria for the clinical and research realms, including categories/bins of variants, structures to guide clinicians and researchers on when to step in, and a systematic approach to decision making about which variants to return, all of which will require an evidence base.
- Structures for support to return incidental findings in clinical care and research are needed.
- The community needs to decide what to report, how to manage reporting, and how we will fund the cost of following guidelines. The costs and benefits associated with implementing guidelines should be considered.
- The process to develop guidelines should be transparent, inclusive, and flexible.
- There should also be deliberation about how best to integrate/consider individual participant/patient preferences.
- The community also needs to consider how to avoid a “race to the bottom” in terms of cost relative to quality.

A variety of resources will be required for successful implementation of guidelines. Infrastructure needs include oversight paradigms and other tools:

- When appropriate, structures for EHR inclusion will be required. Who will decide what information goes into the EHR? Thresholds for inclusion and alerts will need to be developed.
- How will cross-talk between the research and clinical realms be managed? Resources and tools to support data sharing will be needed.
- Finally, funding support will be needed to generate data, track outcome measures, and evaluate the cost/benefit of returning results.

Development and implementation of guidelines requires more research:

- Research is needed to understand return of results and incidental findings in the pediatric context.
- More economic analysis/research is needed.
- The research community needs to increase its efforts/emphasis to include broader populations in research studies.
- Researchers need to extend their study designs, moving beyond hypothetical situations to direct, “needle in the arm” research.
- The community also needs to create space for discussion and “practice” iteration and evolution, as relying on literature alone for dissemination will not keep pace.

All parties (clinicians, institutions, IRBs, participants, patients, policy makers, regulators, researchers) need more education on the return of results and incidental findings. Related research questions include how the parties should be educated and what information should be included. Education will require development of materials that will disseminate information and fill the gaps in knowledge.

Participants need to be included in the conversation as policies are developed:

- The community should understand and anticipate the influence of the Patient Centered Outcomes Research Institute (PCORI) and developing research structures.
- Lessons from other fields, including radiology and the introduction and evolution of the HIV test, should be carefully considered.
- State laws that might be germane to the issues in return of results and incidental findings should be examined, and the effect of the Affordable Care Act should be considered.
- Liability issues and relevant existing case law should be explored. Incentives to share data from the clinical and research settings should be created.
- Regulatory issues, such as the roles of CLIA, the Food and Drug Administration (FDA), the Common Rule, the Health Insurance Portability and Accountability Act of 1996 (HIPAA), EHR standards, and international standards/guidelines should be considered.
- Informed consent is integral to return of results and incidental findings. Research is needed to understand how to effectively execute informed consent and how to address researcher and participant expectations and preconceptions. Best practices should be developed and disseminated.

Next Steps

Workshop attendees might come together in groups or independently to write one or more papers on the issues discussed during the workshop.

Ideas emerging from the workshop will serve as a resource for the research community and inform internal NHGRI discussions about research priorities.