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Return of Individual Results in Epilepsy Genomic Research: A View from the Field

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Epilepsy Return of Results Workshop Participants*

Summary

Genomic findings are emerging rapidly in two large, closely related epilepsy research consortia, the Epilepsy Phenome/Genome Project and Epi4K. Disclosure of individual results to participants in genomic research is increasingly viewed as an ethical obligation, but strategies for return of results were not included in the design of these consortia, raising complexities in establishing criteria for which results to offer, determining participant preferences, managing the large number of sites involved, and covering associated costs. Here, we describe challenges faced, alternative approaches considered, and progress to date. Experience from these two consortia illustrates the importance, for genomic research in epilepsy and other disorders, of including a specific plan for return of results in the study design, with financial support for obtaining clinical confirmation and providing ongoing support for participants. Participant preferences for return of results should be established at the time of enrollment, and methods for allowing future contacts with participants should be included. In addition, methods should be developed for summarizing meaningful, comprehensible information about findings in the aggregate that participants can access in an ongoing way.

Keywords

genetics; pathogenic variants; research ethics; epileptic encephalopathy

Introduction

The Epilepsy Phenome/Genome Project (EPGP), a consortium for genetic research in the epilepsies, was launched in 2007 with 27 enrollment sites in the United States, Argentina, Canada, and Australia.[1] Epi4K,[2] another consortium with close ties to EPGP, was launched in 2011 with the goal of identifying epilepsy-related genomic variants through whole genome or whole exome sequencing in at least 4,000 people with epilepsy, a majority of whom were EPGP participants. Here, we describe the development of plans for return of genomic results to participants in these two closely related consortia, including challenges faced, alternative approaches considered, and progress to date. We also report on a workshop held in San Francisco in July 2016 to seek broader input from clinical epileptologists, genetic counselors, genetic researchers, bioethicists, and patient advocates on questions related to return of results. Our deliberations may be informative for other research groups facing similar challenges.

Consistent with usual practice in 2007 when EPGP began, consent forms specified that individual results would not be returned unless they had a major clinical impact on the participant (e.g., an MRI finding with potentially life-threatening implications). Since that time, however, significant changes have occurred regarding the return of individual research results. Disclosure is increasingly viewed as an ethical obligation, based on fundamental

ethical principles such as beneficence, respect for persons, reciprocity, and justice.[3–9] Moreover, empirical research shows that most participants want to receive individual research results, for both themselves and their children.[10–17] Consequently, new approaches have been developed that prioritize participant preferences, and even allow them to control their own return of results.[18–22]

However, bioethicists have debated this topic vigorously. Some argue that researchers are not obligated to return individual results to participants.[23–28] The primary goal of research is to provide generalizable new knowledge rather than individual benefit, and returning individual results conflates the goals of research with those of clinical care, raising the risk of "therapeutic misconception," in which participants have false hopes of personal benefit and investigators may overstate the benefits of enrollment.[27,29] Also, results obtained in research settings are not subject to the same standards of scientific validity or sample identity verification as those obtained in laboratories responsible for analyses for clinical care (which in the US means laboratories certified under the Clinical Laboratory Improvement Amendment [CLIA]).[26,27]

In the context of clinical whole genome or exome sequencing, the American College of Medical Genetics and Genomics (ACMG) recommends that regardless of the original indication for sequencing, findings be returned for pathogenic variants in 59 genes with clinically significant implications and available treatment or preventive strategies.[30,31] Others have considered the conditions under which these "secondary" findings should also be returned in the research context.[28,32–36] Investigators in the Clinical Sequencing Exploratory Research (CSER) Consortium and the Electronic Medical Records and Genomics (eMERGE) Network argued that research results should be offered to participants if they meet a threshold for clinical validity and "actionability" (i.e., the availability of preventive or therapeutic interventions), and the participant has consented to receive them.[28] However, they also emphasized that participants have a right to decline to receive results, and that while researchers should be prepared to return secondary findings obtained as part of research procedures, they do not have an ethical obligation to actively search for such findings, a view shared by the U.S. Presidential Commission for the Study of Bioethical Issues.[37]

Findings from EPGP/Epi4K emerged in the context of this rapidly changing landscape. In 2013, exome sequencing data from 264 parent-offspring trios ascertained in EPGP revealed *de novo* genomic variants likely to be causal in 14% (N=37) of participants with epileptic encephalopathies (epileptic spasms or Lennox-Gastaut syndrome).[38] Continued analyses are leading to expanding numbers of epilepsy-related findings among EPGP participants.[39–42] Thus, an Epi4K Return of Results Committee was formed to consider what actions should be taken to offer results to participants. Challenges faced by the Committee were discussed at the Return of Results Workshop (Table 1).

Return of Results Workshop

Criteria for deciding which results to return

Consistent with the view that researchers do not have a duty to "hunt" for secondary findings, Epi4K investigators do not plan to offer to return secondary findings, except those identified in the course of analyses directed at our primary study aims (finding genes that influence the risk of epilepsy).[28,37] We also do not plan to return variants of uncertain significance.

For return of primary research results, Workshop participants considered three criteria: clinical validity, clinical utility, and personal utility. Clinical validity includes evidence both that a gene is related to the phenotype and that a particular variant within the gene is pathogenic. For selection of genes in which variants should be considered for return, we decided to follow the criteria of ClinGen[43] (clinicalgenome.org), which include: number of published cases with the correct inheritance pattern and/or type of variant; case-control data if relevant; functional data (e.g., expression profiles, cellular studies, and animal studies); and replication (>2 publications over ≥3 years). For selection of variants to be considered for return, we decided to select those classified as "pathogenic" or "likely pathogenic" based on the ACMG variant interpretation matrix.[44]

The second criterion, clinical utility, refers to the ability of a genetic finding to lead to improved health outcomes such as mortality, morbidity, or disability.[45,46] A key consideration is "actionability" -- i.e., whether the finding will lead to a change in treatment or other aspects of clinical management, such as reducing the need for additional diagnostic tests. Findings judged to have clinical utility will be offered for return.

Receiving a genetic diagnosis may also have "personal" utility, defined as benefits valued by patients that reach beyond clinical utility.[47,48] While reactions are not universal, many families report benefits such as reducing guilt, helping to set expectations about prognosis, informing reproductive decisions, and providing an opportunity to connect with others with the same genetic cause. In a recent study that assessed motivations for genetic testing among members of families containing multiple individuals with epilepsy, "the potential to know if epilepsy in the family is caused by a gene" ranked second highest, reflecting a strong influence of personal utility in motivations for testing.[49] Personal utility is clearly important and should be considered in evaluating results to return; however, because of the costs involved and variations among participants in the value placed on different benefits, priority may be lower for return of results with personal, but not clinical, utility.

While a standardized process is in place for evaluating the clinical validity and pathogenicity of specific variants,[44] evaluation of clinical and personal utility is more complex, requiring regular updating based on the specific context of genomic findings in epilepsy. A group of at least three EPGP/Epi4K consortia members with a combination of expertise in genetics and clinical epilepsy will serve as an expert panel to evaluate the clinical validity, clinical utility, and likely personal utility of each finding.

We also considered whether participants should be informed if no causative variant was identified. Some participants may misinterpret lack of a result as meaning their disorder is not genetic.[50] Also, a "negative" result is less certain than a positive one. Given the rapid pace of gene discovery, a result that appears "negative" today may be reinterpreted as yielding a causative variant in the future. On the other hand, returning some information is consistent with ethical principles of reciprocity and respect for persons, and builds trust in the research enterprise. We therefore considered it appropriate to inform families in which no pathogenic variant was identified that "there is nothing to report at this time that warrants clinical confirmation."

Should CLIA Confirmation be Required?

Workshop participants did not reach a consensus on the requirement of CLIA confirmation for return of research results. CLIA offers two important advantages that protect participants from receiving incorrect information: (1) ensuring high quality laboratory methods and standards for interpretation and (2) protecting the chain of custody of samples, thus assuring that a result is reported to the correct person. Some Workshop participants considered CLIA confirmation essential to avoid the potential for error and participant misunderstanding. In addition, because of uncertainties about the legality and ethics of releasing clinically relevant research results that are not CLIA-confirmed, many IRBs require CLIA certification.

On the other hand, CLIA legislation specifically applies to information that will be used for clinical care, and the process by which research results are returned strongly influences whether they fall into this category.[27] A process that involves medical care providers (e.g., physicians or genetic counselors) raises the likelihood that they will be used to make or inform a clinical decision, and would therefore require CLIA confirmation. Processes in which results are delivered directly to participants (e.g., web-based systems for self-management of research results[18,20] or letters sent from the research team) are less likely to lead to use of the findings for clinical care. Such processes might be appropriate for return of non-CLIA confirmed results (e.g., by making results available with a requirement that participants provide the name of a healthcare provider who could assume responsibility for CLIA confirmation) and would be less costly and easier to use on a large scale, over a long term than those involving delivery by physicians. The feasibility and acceptability of such an approach, however, would depend on the ability to ensure that participants understand the differences between research results and clinical results.

An additional complexity arises from our inclusion of recruitment sites outside of the U.S. Although regulations vary, many countries (including all three of EPGP's non-U.S. sites -- Canada, Australia, and Argentina) do not require the kind of clinical confirmation for return of genomic results required in the U.S.

Empowering Participants to Make Informed Choices

The consent forms used in newer exome or genome sequencing studies either disclose which findings will be returned or ascertain participant preferences for return at the time of study enrollment.[51] However, the original EPGP consent form stated that participants would receive no individual benefits and did not offer them a choice to receive individual results.

Thus, although research consistently shows that most participants want to receive findings, [10–17] and many EPGP participants ask for results despite the consent form's statement that they would not be offered, we have no information about the specific preferences of most of the participants in our study. The challenge we face is how to offer results (which may have clinical or personal utility, and which we believe most participants will want to receive), without causing harm to participants who do not want to receive them. Although re-contacting all participants to ascertain and record their preferences would be ideal, it would be labor-intensive and costly. Moreover, participants' personal information was initially held at the enrollment sites rather than at a central location, and a later effort to centralize this information was successful for only about half of participants. Thus, for many participants, re-contacts need to rely on staff at the enrollment sites, who are no longer supported by the study.

Providing Ongoing Support

Ongoing contact with participants would be beneficial because it would enable the research team to offer them support for understanding and managing the findings. Further, the sequencing results may be reinterpreted over time as new epilepsy-related findings emerge, and we would like to be able to offer these reinterpreted results to the participants. The epilepsy community is well positioned for variant reinterpretation through the Epilepsy Genetics Initiative (EGI) (www.cureepilepsy.org/egi/), a research effort jointly sponsored by Citizens United for Research in Epilepsy (CURE) and the National Institute of Neurologic Disorders and Stroke. In EGI, patients undergoing clinical sequencing are invited to deposit their sequence data, along with some clinical information, in a repository where data are reanalyzed every six months, allowing for discovery of novel genes or pathogenic variants in genes that have recently been published as causative for epilepsy. In the case of clinical sequencing, new findings from the EGI reanalysis are reported back to the physician who ordered the test. However, for participants in Epi4K, return of results from reanalysis presents the same complexities as for return of the initial findings.

Need for Research

An important conclusion of the Workshop is that more research is needed on processes related to return of results in genomic research. Although the plan we developed for return of results in Epi4K is practical and ethically acceptable for a small number of participants with specific findings, the issues we faced in our deliberations need to be addressed more generally. Our current plan would be difficult to scale up to the larger number of participants with findings from our ongoing research, and funds for this work remain a significant obstacle, since they were not included in our original research budget.

The need for CLIA confirmation presents particular challenges because of the costs involved. Hence, one potentially fruitful area of future research would be what processes could be used to return research results that are not CLIA confirmed without causing harm. Returning non-CLIA confirmed results would clearly require assurance that participants understand that results should not be used in clinical care; rather, they are research findings that may help to inform choices about clinical testing. This approach is likely to be more acceptable if the method of return clearly differs from clinical care (as in, for example, a

web-based system like My46).[19] Obtaining the perspectives of research participants, providers, and IRB members would be very helpful in addressing these issues, as would empirical data on participant understanding, psychosocial impacts, and clinical impacts related to return processes that include or exclude CLIA confirmation.

Additional areas for further research include the question of whether, and if so how, to return negative results, the utility of return mechanisms that rely on physicians who may not have training in genetics or experience in returning such results, and optimal methods for participant education and engagement.

Progress in Epi4K

The Epi4K Return of Results Committee decided to develop a plan to return results to participants from a single site, and to use this experience to inform plans for participants at other institutions. We selected UCSF for this pilot because it is the original source of the EPGP study and houses the EPGP database. We focused on causative *de novo* variants in participants with epileptic encephalopathies reported in the first paper,[38] six of which were in participants from UCSF (in *ALG13, DNM1, GABRB3, GNAO1, GRIN2B,* or *SCN1A*).

These variants clearly met our criteria for return to participants. All are already included in gene panels offered by clinical testing laboratories, and some have important clinical implications. In addition, for these severe childhood epilepsies, the results are likely to have important personal utility, ending the “diagnostic odyssey” by providing an answer about what caused the child’s epilepsy, and informing reproductive decisions.[52] In other Epi4K analyses, decisions about return of results are likely to be more complex. For example, in families containing multiple individuals with common forms of epilepsy, the clinical utility of genomic variants discovered may be less clear, and the concerns of multiple family members will need to be considered.[1,2,42,53,54]

Initially, we considered protecting participants’ right “not to know” by sending a letter to all participants informing them that 10–15% of participants had a finding, and advising them to contact their physicians if they wanted to learn more. However, we rejected this idea because it could raise false hopes or anxiety for the 85% of families without findings, and the UCSF IRB agreed. We also recognized that this approach would impose an untenable burden on the referring physicians (who would need to assume responsibility for providing pre-test genetic counseling, CLIA confirmation, and post-test disclosure). Clinical testing is available in some, but not all, of the 27 EPGP recruitment sites. As it becomes more widely available, it will offer more options for participants and their local physicians to verify research findings.

In addition, we had extensive discussions regarding the role of the treating physician. We faced a significant problem because we had not asked participants to designate a physician who they authorized to receive the results, and could not assume they had an ongoing relationship with the physician who had enrolled them in the study. We did not consider it ethical to return a participant’s results to a physician without the participant’s consent, and this perspective was shared by the UCSF IRB. An additional complication was that some

participants were recruited through a national recruitment campaign,[55] rather than through any physician. In fact, this was the case for all six families in our pilot study.

Based on these concerns, we decided to send a letter only to participants who had a genetic finding that we considered to have clinical utility. To protect the participants' right "not to know," the letter stated that findings had been obtained in 10–15% of participants, but did not explicitly state that they were part of that group. This plan held the risk that some participants would learn they had a finding even if they had not chosen to receive it (through communications among participants about receiving or not receiving a letter). However, we judged that in this case, this risk was warranted because participants were likely to want to receive the results, and the decision to pursue them further was still left to the contacted family.

Our initial protocol included pre-test (or pre-disclosure) counseling to ensure that participants had sufficient knowledge and support to be able to make an informed choice about whether to receive findings. However, when families were contacted, they responded that they did not want pre-test counseling, and wanted further involvement only if we could tell them that they definitely had a finding. We consulted the IRB about this new information, concerned about informing the families they had a finding that had not been CLIA-confirmed. The IRB concluded that we could inform them, but that we should still CLIA-confirm the results and return them in a post-test disclosure session with a genetic counselor. The revised plan for return of results, approved by the UCSF IRB, includes written educational materials for participants to review when deciding whether to receive results; pre-test counseling is optional (Table 2).

All six families expressed interest in receiving the genetic results. One had already undergone clinical genetic testing and learned their child's genetic result. Another expressed interest in receiving results but did not return the consent form to proceed with CLIA confirmation, despite multiple follow-up attempts. The other four families gave consent to confirm their results, and three of the four returned their saliva kits and received their results.

In the pilot, all patient contacts were initiated by the EPGP Project Coordinator, who then arranged for post-test counseling through a USCF genetic counselor. Costs for re-contacting the families, CLIA confirmation (obtaining new samples and clinical laboratory analysis) and post-test genetic counseling were not included in the project budget and had to be covered by a separate discretionary account, leaving open the question about how this process could be undertaken for other Epi4K participants.

Lessons Learned

The landscape has changed substantially since EPGP was launched; hence, it may not be surprising that in retrospect, we recognize that some procedures should have been done differently. We have been stymied by the costs involved in return of results to EPGP participants more broadly and are considering what sources of funding might be available, either through philanthropy or a grant designed to investigate the process of return of results explicitly. Our experience illustrates the importance of including a specific plan for return of

results in the study design, with financial support for obtaining clinical confirmation and providing ongoing support for participants. In consortia involving sites from multiple countries, plans for return of results should be specified in advance for each site, with respect for local policies and regulations. As previously recommended,[37] participant preferences for return of results should be ascertained at the time of enrollment, including the types of results participants want to receive and their preferred methods of communication (e.g., by specifying the name of a medical provider). Prospective methods for allowing future contacts with participants should also be included. Finally, methods should be established for summarizing meaningful, comprehensible information about findings in the aggregate that participants can access in an ongoing way (e.g., via a web site).[56]

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Key points

- Disclosure of individual results to participants in genomic research is increasingly viewed as an ethical obligation.
- Criteria for selecting genomic findings to offer include their clinical validity, clinical utility ("actionability"), and personal utility.
- Participant preferences for receiving results and their preferred methods of communication should be established at the time of enrollment.
- Covering costs for obtaining clinical confirmation and providing ongoing support for participants may present significant challenges.
- Additional research is needed on processes related to return of results in genomic research.

Table 1.

Questions Addressed in Return of Results Workshop

1. What criteria should be used to evaluate which results to return?
2. Should CLIA confirmation be required?
3. What is the best way to empower research participants to make the best decisions for themselves about which results to receive?
a. What processes should be used to document participant preferences for return of results (which was not done originally) and obtain informed consent?
b. What is the role of pre-test genetic counseling?
c. What approaches should be used for genetics education?
4. What processes should be used to communicate results to the participants?
a. What is the role of the physician?
b. What is the role of disclosure/post-test genetic counseling?
5. How should the multi-site nature of the project be handled, given that multiple IRBs are involved and contact information for many participants is maintained at the sites?
6. How should changes in interpretation of the results over time be handled? Should they be communicated to research participants and if so, how?
7. What approaches can/should be used to provide ongoing information and support?
8. How should costs be handled, given that the project's budget did not include funds for return of results?

Table 2.

Essential Elements of Return of Results Plan for Six Initial Epi4K Participants

Initial contact	Letter sent to participants who have a finding, informing them that they have a finding believed to be causally related to their child's illness. Follow-up phone call made two weeks after the mailing.
Right not to know	For the follow-up phone call, telephone script used that provides participants the chance to opt out at several points if they prefer not to know their genetic finding.
Consent form	Each participant sent a short consent form via email that can be signed electronically. Coordinator explains the project in detail and answers questions, to assure participant is fully informed, before proceeding. Participants who provide consent proceed to the next step.
Pretest counseling	Pre-test genetic counseling available, but not required.
CLIA confirmation	CLIA confirmation required, to minimize the risk of participants' receiving an erroneous result.
Sample collection	New sample for CLIA confirmation collected via saliva kit mailed to participant's home with prepaid return shipping, to reduce participant burden.
Genetic counseling	Results returned in a disclosure session with genetic counselor before the participant receives a copy of the CLIA confirmed result. In case the participant's current provider is not knowledgeable about epilepsy genomics, the genetic counselor is also available to discuss the finding with the provider.
Educational materials	General information sheet about genetic findings sent to participants for review when they are deciding whether to receive information. One-page information sheet given to participants with their CLIA confirmation, summarizing what the genetic counselor reviews with them.
Qualitative interviews	In-depth qualitative interviews carried out to assess participants' thoughts, feelings, and behaviors approximately 1 month after the return of results