

**National Institutes of Health (NIH)
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)**

Return of Genetic Results in Kidney Research—Emerging Practices Workshop

July 31, 2023

EXECUTIVE SUMMARY

Returning the results of genetic testing to research participants involves many important considerations. It is a new practice for many researchers, and consensus about the best way to return results continues to evolve. Because there is no uniform way to return results from research, choices often must be made on a study-by-study basis, and the ethical responsibilities must be balanced with the resources available in each case. This workshop aimed to promote discussion and sharing of experiences and challenges regarding the return of genetic results in research settings to identify issues research teams should address as they develop appropriate return-of-results plans.

Framework and Rationales for Return of Results

Genomic medicine promises to improve clinical care for nephrology and kidney disease patients. Efforts to return genetic results to research participants are increasing, but researchers currently do not have clear guidelines to follow. Genetic results are returned for different reasons in research and in clinical care. Research focuses on increasing general knowledge for the benefit of society, whereas clinical care centers on benefitting specific patients and includes the patient's best interest as a key responsibility. A report published by the National Academies of Sciences, Engineering, and Medicine emphasized the importance of studies offering return of results, while upholding the right of each individual participant to decide whether to receive any results offered and ensuring that results are clearly communicated to help research participants understand the meaning of the results and the implications for their health care. Researchers also need to include diverse populations and ensure the validity and reliability of results that are being returned, with the aim of affecting clinical care.

Several types of kidney-related genetic results can be returned. Monogenic diagnostic findings identify a single variant in a gene that significantly influences the chance of having a kidney disease. Genetic risk factors identify a genetic variant that increases the risk of disease, which might be more or less prevalent among some populations. Polygenic risk scores provide a single score that combines interactions among many genetic variants, each with a small effect, that together cause an increased risk for a particular disease. Existing knowledge of polygenic risks often has relied on datasets with overrepresentation of white European ancestry groups, making the results less generalizable for other racial and ethnic groups. Another possible result is identification of variants of unknown significance, which involves changes in genes with unclear clinical impact. These could have a range of interpretations or change in meaning over time. Genetic results also may include secondary findings, such as genetic variants of potential medical value that are unrelated to the primary reason for which participants undertook a study.

Each study defines its own workflow for returning results. Studies may need to re-consent participants if the initial study did not include an option for returning results or if pediatric

participants have reached adulthood since the study was conducted. Researchers also must ensure that participants understand the meaning of results and what actions can be taken. Genetic counselors are scarce, so researchers must consider whether they have a responsibility to provide counselors or be aware of what alternatives to genetic counseling exist and, how and when to best use them. There are also issues of equity issues such as result validity and affordability, accessibility, and access to follow up care that need to be considered.

Current Return of Results Practices

In the NIH [All of Us Research Program](#), participants consent to share data with the program and decide whether they want to be contacted in the future with specific types of DNA results; the consent process allows participants to change their mind at any time. Currently, the program offers two reports: one on hereditary disease risk and one on genes that may interact with medications. Participants whose genetic reports identify a pathogenic or likely pathogenic variant are asked to connect with genetic counselors, who are always available within 48 hours after the participants are notified of the report. Pathogenic findings are confirmed with a second assay, allowing participants to use that information to seek clinical care. Ensuring that any participant who receives a pathogenic finding can have the result clinically verified is important for equity.

The [Cure Glomerulonephropathy Network](#) study was designed to include return of results; the consent forms include optional provisions with a broad framing for returning results, which can encompass both kidney disease results (diagnostic or increased risk) and secondary findings. Sequencing participants' data was a multi-step process. The study began returning genetic results to a highly diverse cohort, assess barriers to implementing the workflow for return of results, and assessing the impact of the return of genetic results on clinical decision-making and participant well-being.

[The Nephrotic Syndrome Study Network \(NEPTUNE\)](#), which started in 2010, initially did not plan to return results, but added whole-genome sequencing when it became technologically and economically viable. For practical purposes, NEPTUNE is reconsenting only participants with identified pathogenic or likely pathogenic variants, but reaching patients to re consent them has been a major challenge, and NEPTUNE researchers must consider whether devoting a substantial amount of the study's limited resources to return of results will hinder overall research progress.

The [Kidney Precision Medicine Project](#) developed its return of results proposal with a working group that included patients, ethicists, and clinicians; consultation from experts; and workflows that account for many considerations. If initial results are positive for concerning variants, participants may provide a second sample for Clinical Laboratory Improvement Amendments (CLIA) confirmation of the results. The consent states that the second sample will be placed in the patient's medical record, but participants can choose whether to add CLIA-confirmed apolipoprotein L1 (*APOLI*) gene results, which indicate an increased risk for chronic kidney disease, to their medical record; this decision was based on community apprehension about whether *APOLI* results would affect insurance coverage.

Special Issues in Returning Results

The [Chronic Kidney Disease in Children \(CKiD\)](#) study, which started in 2003, initially prioritized privacy protection, so the samples in its genome biobank were deidentified to facilitate research, and participants were informed that no genetic results would be returned; however, these paradigms no longer reflect the desires of participants. CKiD partnered with pediatric ethicists, convened a parent advisory council, and developed a framework for disclosure that requires parent or caregiver permission and participant assent when they are old enough to have the capacity for adult-like decisions, usually about age 13. Participants are contacted for consent when they are 18 years old. CKiD also is developing educational materials and a survey that will be used to implement a study-wide return of results process. The time, effort, and funding required for returning results necessitates ongoing NIH support.

The [APOLLO](#) study, which focuses on *APOLI* results in kidney transplantation, included return of results in its protocol development, but the study was required to develop an independent CLIA laboratory to return results responsibly. Its community advisory board and steering committee emphasized the importance of returning *APOLI* genotypes to participants and providing education regarding the implications of the results. Participants receive their results directly and then can decide whether to inform their physicians or families.

The [Electronic Medical Records and Genomics Phase IV \(eMERGE-IV\)](#) study concentrates on polygenic and monogenic risk assessments for 10 common conditions. In the absence of high-quality, equitable polygenic risk scores for these conditions, eMERGE-IV developed its own scores and was able to demonstrate adequate performance across all ancestral groups. Participants receive CLIA-confirmed results and a genomic integrative risk assessment that is integrated with family history to provide context, and positive results are returned through genetic counselors. Individuals with high-risk results receive recommendations for education, screening, and special tests. In many of the studies that currently return results, costs must be covered by supplemental funding, but building return of results into the design from the beginning allows appropriate budgeting.

Genetic Counselor Panel—Experience on the Ground

Many of the small number of genetic counselors currently working in the United States are based in large cities, and these limitations in geography and availability require that investigators think creatively about when counselors are required, when to deploy clinicians with genetics experience, and what other options are available. Some biobanks offer participants the option to provide an additional sample for CLIA confirmation, but the time between consent and return of results can be very long, and research programs often cannot cover the costs of follow-up care. Returning secondary findings can help researchers better understand variant expressivity and penetrance, and ensuring that all patient communications are fully accessible is critical.

Use of creative counseling strategies is highly dependent on physician comfort and education, so any strategies must be designed to be accessible and easy for physicians to integrate into their workflow. Counselors also must set clear expectations with patients, particularly when delivering information about results with unclear implications, such as variants of unknown significance. Research suggests that participants have mixed feelings about receiving uncertain results—

participants often expect research to resolve uncertainty and believe researchers understand results thoroughly, so researcher transparency about their lack of understanding is important.

Community Engagement and Patient Panel

Although the association between *APOLI* variants and kidney disease in people of West African ancestry is known, researchers do not yet know how to use that awareness to reduce the burden of *APOLI*-mediated kidney disease (AMKD). Researchers need to increase awareness; identify people with, and those at risk for, AMKD; and increase participation of minorities in clinical trials. Community engagement is a critical aspect of this process. When people are contacted by the Community *APOLI* Research Engagement (CARE) program, they usually receive information about the study politely but cautiously, but their interest increases after researchers explain its importance. Initially, the CARE study did not plan to return results, but the community advisory board emphasized the importance of returning results to build trust. Response to the genotype varied by health status—people with AMKD express strong interest in knowing their genotype, saying that knowing gives them a feeling of relief and reduces self-blame. Healthy participants have more mixed opinions, often including anxiety and questions about insurance.

During the patient panel, volunteers recounted their experiences with genetic testing for kidney diseases in clinical practice, non-research settings. Patient panelists at times received a series of misdiagnoses, experienced mistreatment from providers advocating the tests, and were offered genetic tests that were not necessarily affordable or accessible. Most volunteers had shared some of the information from their tests with family members, but additional testing for those family members often was cost prohibitive. In many cases, receiving information about genetic risk encouraged participants to be proactive about their or their family's health, but few options for clinical treatment were available. Panelists emphasized that managing patients' expectations of genetic testing is important; patients often expect answers and receive more questions, and clinicians or researchers may not have the information patients need for support or may encourage the patient to make significant decisions based on uncertain information. Having access to a counselor who can explain the results and establishing connections to other families dealing with the same disease are important. Clinicians' abilities to communicate and each individual clinician's ability to understand genetics affected each volunteer's experiences, so the panel emphasized the importance of finding ways to communicate complex scientific information (including the uncertainty of many results) to people without scientific backgrounds and understanding how uncertain statements sound from the patient point of view.

Breakout Sessions

Breakout sessions focused on the responsibility and priorities for return of results, the responsibility for validation, the responsibility for genetic counseling and follow-up, and the responsibility for equity and inclusion. Highlights of the discussions included the following:

- Clear, informed consents that are broadly accessible, including in multiple languages, are important.
- Input from individual participants is key to finding the right balance in returning results.

- Genomic analysis has the potential to return a variety of actionable findings, but returning results always will need to be balanced with practical consideration, such as limited resources and expertise, and the balance will be resolved differently depending on the nature of each study. Participants often express the desire to have all results returned, but this is not always feasible for studies.
- Validation often is also limited by resources; CLIA is the best current validation, but even participants at the research level may want clinical validation.
- Researchers need to be sensitive to cultural considerations as they design return of results processes and understand that people may respond differently.
- Tensions often persist between research and clinical practice, so actionable results must be returned with careful processes.
- Devoting resources to returning results leaves fewer resources for research; a careful balance is necessary.
- Offering multiple options for how results should be returned is best. Options for reinterpreting results when new data emerge over time must be provided in a way that does not hinder the ability to make future discoveries.
- Not all participants can afford to have results clinically validated if the study does not provide support, which can lead to disparities.
- Responsibilities for returning results are very study dependent; written results may be appropriate with simple studies, but genetic counselors are often needed for in-depth discussion. Participation of genetic counselors throughout the study will support the responsible return of results, and future studies should include a budget for genetic counselors, if appropriate.
- The responsibility to provide culturally appropriate return of results requires recognizing intersectionality and consideration of a variety of factors. Researchers must be empathetic and humble, and communities should be consulted frequently.
- Patients have the right to know their health information, so decisions about return of results should be made with patient involvement.
- In many cases, the responsibility to return results goes beyond the individual; the community should be informed about what has been learned, and results should be disseminated in publications that the community will read.
- Researchers have an obligation to care for communities that are disproportionately affected by poor health and that usually do not benefit from health advances.

Summary and Closing

Genetic results can significantly improve the quality of diagnosis and health care, but the process involves many important considerations. Patient autonomy must be prioritized, and patients, genetic counselors, clinicians, and scientists must collaborate from a study's inception. Return of results processes need to be planned in advance based on the goals of the study to avoid the challenges associated with changing processes later. Researchers must balance ethical and

practical considerations and communicate with participants clearly and thoroughly. The process will continue to evolve with increasing knowledge, education, and technological advancement, but return of results practices always will need to be tailored to each study and individual participant.

Organizing Committee

- Ali Gharavi, M.D. (Co-chair)
- Maya Sabatello, Ph.D., LLB (Co-chair)
- Wylie Burke, M.D., Ph.D.
- Nanibaa' Garrison, Ph.D.
- Ingrid Holm, M.D., M.P.H.
- Carol Horowitz, M.D., M.P.H.
- Nichole Jefferson
- Afshin Parsa, M.D., M.P.H.
- Glenda Roberts
- Robb Rowley, M.D.
- Clesson Turner, M.D.

Moderators

- Meg Hager, M.S., M.P.H., CGC
- Hila Milo Rasouly, Ph.D., M.Sc., GC
- Matthew Sampson, M.D., M.S.
- Wendy Uhlmann, M.S., CGC

Study Presenters

- Barry Freedman, M.D., FACP
- Krzysztof Kiryluk, M.D.
- Opeyemi Olabisi, M.D., Ph.D.
- Ana Claudia Onuchic-Whitford, M.D.
- Craig Wong, M.D.
- Bessie Young, M.D., M.P.H., FACP, FASN

Genetic Counselors Panel

- Emma Perez, M.S., CGC
- Mary-Beth Roberts, M.S., CGC
- Catherine Wicklund, M.S., CGC

Patient Presenters and Panelists

- Andrea Alvarez
- John Brandon Bayton, Jr.
- Jennifer England
- Nichole Jefferson
- Jennifer Jones
- Sharon Lagas
- Denay Richards
- Curtis Warfield
- David White
- Trinisha Williams, M.P.H., LM