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Ethical and Policy Considerations for Genomic Testing in Pediatric Research: The Path Toward Disclosing Individual Research Results

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Abstract

DNA is now commonly collected in clinical research either for immediate genomic analyses or stored for future studies. Many genomic studies were previously designed without awareness of the ethical issues that might arise regarding the disclosure of genomic test results. At the start of the Chronic Kidney Disease in Children (CKiD) Cohort Study in 2004, we did not foresee the advent of genomic technology or the associated ethical issues pertaining to genetic research in children. Recent genomic studies and ancillary proposals using genomic technology stimulated the CKiD investigators to reassess the current ethical and policy environment pertaining to genomic testing and results disclosure. We consider the issues pertaining to next generation sequencing and individual results disclosure that may guide current and future research practices.

Introduction

The Chronic Kidney Disease in Children (CKiD) Study was designed to evaluate risk factors for chronic kidney disease (CKD) progression and the associated impact of CKD progression on the cardiovascular disease risk factors, growth, and neurocognitive function of children with mild to moderate CKD.¹ When enrolling study participants, we obtained general consent for participation in CKiD and also sought specific parental permission to store deidentified blood, urine, and DNA for future studies. The permission to store DNA for future research was broad and it indicated that no individual results would be disclosed to participants or their parents.

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Note: Based on information in Downey et al,¹⁴ except where indicated.

Abbreviations: CLIA, Clinical Laboratory Improvement Amendments; IRB, institutional review board.

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Since CKiD was launched in 2004, there have been significant advances in genomic technology. These have provided new opportunities to explore genetic associations with disease.² The initial genetic studies in CKiD, conducted under the initial broad consent, focused on the prevalence of pathogenic mutations in genes known to be associated with kidney disease.^{3–5} More recently, efforts have focused on large-scale genotyping studies^{2,6} that provide more information about each participant's genomic characteristics. Some of these yield information that is relevant to kidney disease research, whereas some provide information about other diseases and risk factors.

Using genome-wide genotyping data, CKiD investigators surveyed the frequency of genetic imbalances caused by copy number variants among children with CKD. They found a high burden of genomic imbalances in the cohort with pathogenic variants found in genes known to be associated with kidney diseases.⁷ Incidentally, some participants in this study who had an unknown cause for their CKD were discovered to have an underlying genetic diagnosis; others had a clinical diagnosis that was discordant with the genetic diagnosis. Although parents of participants were informed that no individual results from genetic testing would be disclosed, the discovery of an underlying genetic diagnosis for the participant's CKD might have been important to the families, prompting CKiD to consider when disclosure of genetic research results might be appropriate for future studies.

The prevailing paradigm regarding genetic research has historically been that of nondisclosure of research results to participants. Expressed concerns related to the impact of sharing information that had uncertain clinical value. Furthermore, there were concerns regarding possible genetic discrimination.⁸ Thus, for most genetic research, a policy of nondisclosure of individual results to participants allowed some level of privacy protection and avoided unnecessary harms. To protect participants from potential harm, it was common for research studies to deidentify biospecimens so that results could not readily be linked back to the individuals.⁹ In turn, individual research results were not disclosed to the participant and typically described in aggregate to ensure privacy. Similar to CKiD, other pediatric kidney disease studies collecting DNA for research have all had similar policies of nondisclosure of unvalidated genetic research results to participants.^{10–12}

In the ensuing decade, the practices pertaining to the disclosure of genetic results to participants have evolved. As genetic testing becomes more familiar to scientists and the public, investigators face growing pressure to disclose genetic findings that have not been validated or confirmed by other studies. Institutions that fund research, many of them public, are now asking investigators and research studies to evaluate the opportunities and challenges of disclosing individual research results for current and future studies (Box 1).¹³

The longitudinal design of CKiD has resulted in a longstanding cohort of investigators, study participants, and their parents who have contributed greatly to the study design and outcomes. Thus, the CKiD investigators now have a unique opportunity to consult with study participants about potential changes in the study design as it relates to genetic investigations. We have begun to consider how to evolve in line with the changes in policy and public attitudes that have taken place regarding genomic testing. In this article, we share how we are approaching the issues pertaining to disclosure of individual research results. We

discuss the establishment of the CKiD ethics committee and relevant policies regarding research results disclosure to help guide pragmatic decisions. For a more comprehensive examination of the issues pertaining to the disclosure of individual research results, we refer the reader to the report by the National Academy of Sciences, Engineering, and Medicine (NASEM).¹⁴

Next-Generation Sequencing in Clinical Care and Implications for Research

Next-generation sequencing (NGS) generates detailed and comprehensive data across an individual's genome. NGS has become affordable and therefore more accessible in both clinical and research settings, heralding what some have called the "era of genomic medicine."¹⁵ Although there have been research studies proposing NGS, the CKiD Study has not committed to perform large-scale NGS projects without in-depth consideration of the ethical and policy ramifications associated with these technologies.

With NGS, we have access to both the specific genetic variants being sought and incidental genetic information that may prove to be important for current and future health. The American College of Medical Genetics and Genomics (ACMG) has curated a list of highly penetrant genetic variants known or expected to be pathogenic, for which early identification may prevent current or future morbidity; these are referred to as secondary findings. For example, BRCA1 and BRCA2 are associated with future risk for breast and ovarian cancer. The ACMG initially recommended that clinical sequencing laboratories analyze and disclose these specific secondary findings when NGS is conducted (Table 1).^{15–18} These conditions and genes are considered both clinically important and actionable. Following criticism that patient involvement is necessary,¹⁹ the ACMG subsequently revised its guidelines to allow patients to decide whether they would like to receive this information.¹⁸

The ACMG's clinical policy for disclosure of secondary findings resulted in particular controversy when applied to children.^{8,20} The recommendations regarding disclosure have challenged the traditional approach to defer the testing of children for adult-onset conditions (as is the case with BRCA1 and BRCA2) until those children become adults.²¹ Reasons to defer testing for adult conditions include the potential psychological burden associated with knowing the risk for future disease and protection of the future autonomy of the child to decide about the sharing of secondary findings for themselves later as an adult. Nevertheless, the ACMG suggested that these concerns were outweighed by the "potential benefit to the future health of the child and the child's parent".¹⁵ For instance, it is argued that if a child carries a pathogenic gene variant of a dominant condition, there is a strong probability that one parent also does. Thus, disclosure of the information may lead to prevention of an adverse outcome in one of the parents.¹⁵ At this time, parents are considered to be in the best position to determine the magnitude of benefit of secondary findings that may arise from clinical sequencing for themselves and their young children.^{21,22}

A proposed ethical framework for disclosure of secondary findings from NGS suggests that health care providers, parents, and the patients all have important roles in weighing risks and benefits of results disclosure when clinical NGS testing is being conducted.²² Health care providers who are ordering NGS testing have an obligation to support the informed

permission process for parents and assent for children and adolescents regarding the disclosure of results from clinical sequencing. Although certain families may opt not to receive secondary findings from NGS, there should be a discussion of the types of NGS results that the clinician may be obligated to disclose. These categories include: (1) findings related to the specific diagnosis of the clinical condition that is prompting the testing (regardless of whether it is treatable), (2) risk assessment for early-onset modifiable conditions, (3) risk assessment for later-onset conditions when the risk is modifiable during childhood, (4) pharmacogenomics results with immediate clinical application, and (5) secondary findings of life-threatening conditions.²²

Of course, these clinical guidelines and ethical standards regarding clinical sequencing have important implications for researchers. Given that the technology is affordable and widespread, investigators who collect DNA to store in biobanks for future testing need to assume that there will be later requests to use these stored samples to perform NGS. Those who are actively using NGS technologies for discovery will need to discuss with colleagues and stake-holders a plan related to secondary findings, as well as other clinically important findings, and consider if, when, and how disclosure may or may not be an integral part of their research activities.²³

Individual Research Results Disclosure: An Uncertain Path

As patient care strategies increasingly emphasize personalized medicine with large-scale genotyping of populations, there is more attention focused on policies pertaining to ethical and responsible disclosure of individual research results that are as yet variable across countries.^{23–25} The United States,¹⁴ Canada,²⁶ and Japan²⁷ have committed to develop policies for the disclosure of research results back to participants. In contrast, whereas many European organizations acknowledge the importance of this issue, they have identified significant barriers to policy development due to the lack of guidelines, legal framework, and infrastructure.²⁸ In the United Kingdom, attitudes toward the disclosure of secondary findings from genomic screening appear less favorable at this time.²⁹

There have been prior working group reports pertaining to the disclosure of research results for genomic testing.^{13,26,30,31} To date, the NASEM report is the most comprehensive, providing ethical rationale and recommendations for all stakeholders involved in research. The recommendations from the expert panel were intended to help: (1) support decision making about disclosure of results on a study-by-study basis, (2) encourage high-quality individual research results, (3) develop understanding by participants of individual research results, and (4) refine and harmonize current US regulations.¹⁴

The CKiD Ethics Committee

The CKiD Study established an ethics committee in 2018 comprising members from the scientific steering committee and bioethicists to determine when it might be appropriate to disclose individual research results to CKiD participants. To that end, the ethics committee has convened a parent/participant advisory committee (PAC) to form a collaborative partnership. Such partnerships have been demonstrated to be valuable in other research

paradigms.³² We anticipate that parents and our older CKiD participants will provide important perspectives on which genetic results should be disclosed and the process by which this information is relayed. Also, the CKiD ethics committee and the PAC will also have to consider how to improve the consent process regarding how families (and older participants) may or may not opt to receive results of genomic testing and potentially other research results prospectively.

Disclosure of Research Results

CKiD and the ethics committee are building capacity to address the existing challenges pertaining to the disclosure of individual research results. Parents and participant representatives of the PAC have been asked to share their thoughts regarding participant needs, preferences, and values in the decision-making process. The PAC will provide critical input as we consider the institution of a results valuation approach to help determine which individual results should be offered to the parent/participant.³³ With a result-evaluation approach, the disclosure of research results is contingent upon the results: (1) being analytically valid and (2) having clinical utility to the participant.³³

Analytic Validity

In the United States, analytic validity is ensured by the Clinical Laboratory Improvement Amendments (CLIA) of 1988. To meet CLIA quality standards, clinical laboratories must satisfy a number of criteria to maintain accreditation. Importantly, they must have processes that minimize biological specimen mislabeling and mishandling to ensure that patient samples are not confused with one another, which may lead to serious errors.¹⁴ CLIA certification is required for all laboratories testing human samples for clinical care, but not required for research studies. Misabeled samples in research studies may not affect aggregate results on the whole but are significant issues concerning individual research results. Central to the concern regarding disclosure of individual research results pertains to errors in specimen labeling and handling.¹⁴ If results from mislabeled specimens are provided to the incorrect individuals, participants may be exposed to a variety of potential harms. NASEM has proposed the development of a quality management system for research laboratories to address this problem.¹⁴ Until systems for overseeing quality in research laboratories are ubiquitous, research studies should consider using CLIA-certified laboratories for all genetic samples initially or do so only for confirmatory testing.³⁰

Clinical Utility

A clinically useful result may be important to the physical or psychological well-being of the participant, to reproductive decision making, or to life planning of the participant.³³ The results considered clinically useful may differ depending on the perspective of the physicians, scientists, or the participant. Clearly, secondary findings that are strongly associated with actionable conditions would fit in a category of clinically useful to all stakeholders. However, there may be other findings with personal value to the parent or participant that may not be considered important or useful to the investigators. Incorporating the needs, preferences, and values of parents and participants from CKiD will be important to the development of a participant-centric approach toward disclosure of research results.

At this time, CKiD is actively reviewing and considering “best practices” pertaining to disclosure of secondary genetic findings and other research results of potential value to participants and their parents. One such model already in practice is the Boston Children’s Hospital Gene Partnership (GP). An oversight board for the GP brought together a multidisciplinary team that developed guidelines regarding the disclosure of individual research results (Fig 1).³⁴ The guidelines encompass actions across a broad age range for participants, including a position in which the participant has come of age and may opt to receive their own information, as discussed next.

A designated committee should evaluate and define criteria to help guide possible disclosure of analytically and clinically valid research results. If there are results generated from NGS, the committee will need to determine whether, based on the study design, resources, and preferences of the participants, to disclose results from the ACMG list of secondary findings. Also, the committee may expand the disclosure criteria to include results pertaining to the cause of kidney disease, especially when the clinical diagnosis was unknown,⁷ or increased genetic susceptibility to CKD (eg, high-risk genotype for APOL1)⁵ or comorbid genetic findings that might prompt increased neurocognitive and educational screening with conditions associated with both CKD and mild cognitive impairment.³⁵ Some of these results may not meet scientific thresholds for clinical validity, but such information may be thought to have personal value as expressed by the CKiD PAC and may be offered for disclosure. However, results of uncertain clinical significance may not be disclosed due to low clinical utility, even if the participant had opted to receive their genetic research results. Beyond the GP guidelines, there are recommendations for mandatory disclosure of childhood-onset conditions for which medical treatment during childhood will ameliorate the future health risk of the participant.^{15,26,36} Clearly, further discussion is needed to develop a consensus among the CKiD stakeholders, and possibly with other nephrology research consortia performing NGS in their studies.

Informed Consent

While the CKiD Study considers these issues, it must concurrently reassess the informed consent process, particularly as it relates to genomic testing and options for disclosure of individual research results. The rationale behind informed consent for adults is to respect adult preferences and decision making, as well as allow for protection from adverse consequences.³⁷ For clinical decision making when a child is involved, the alternative concepts to informed consent are those of parental permission and child assent.³⁷ Adolescents who have the capacity for adult-like decisions should be offered assent for disclosure of individual research results.²²

Similar to the CKiD Study, Boston Children’s GP is a longitudinal study of children. In its approach toward informed consent for results disclosure, the GP has weighed the competing needs of respecting the “child’s future autonomy and parent’s duty to act” in the best interests of their child, offering a paradigm for results disclosure.³⁴ Results are offered for disclosure depending on the age of the child and preferences set by the parent and/or participant, as noted in Figure 2. At younger than 13 years, genetic results are disclosed based on the parental preference. From age 13 to younger than 18 years, the preference of

both the parents and the pediatric participant are taken into account. Presumably, the lower threshold of 13 years is the age at which participants would be developmentally capable to decide on whether to receive genetic research results. However, empirical studies demonstrate that at 12 years of age, most children are competent to make decisions about clinical research.³⁸ When pediatric participants are competent to make decisions but not yet 18 years old, both parent and participant preferences for disclosure must agree. If there is disagreement, results are not disclosed, with some exceptions as determined by the designated committee. At older than 18 years, the participant's preference for disclosure is accepted.

In a longitudinal pediatric study such as CKiD in which many pediatric participants "age out" of their pediatric years, some continue active participation or are involved in telephone follow-up, some have been lost to follow-up, and some have either passively or actively disenrolled. When a participant becomes an adult while actively engaged with research, it is feasible to readdress consent with the young adult. A more challenging situation is the scenario in which participants have disenrolled from the study or have been lost to follow up. In this setting, there are ethical and logistical challenges to obtain consent from former participants for ongoing use of their data and samples for research. When feasible, adults should be asked for permission for ongoing use of their data and samples collected as pediatric participants.³⁹ However, there are questions as to whether there may be continued use of data and samples from participants who are inactive in the study and cannot be reached. When former participants who are adults cannot be located, it is generally acceptable to continue conduct of research using data and samples obtained during childhood.³⁹ Under US regulations, non-interventional research may qualify for waiver of consent or designated as nonhuman individual research given that the samples are deidentified (Box 2).⁴⁰

Permissions for disclosure of genetic research results may require different approaches to consent at the age of majority depending on the design of the research study.⁴⁰ For young adult participants who are actively engaged in research, readdressing consent to consider options for disclosure of genetic research results is feasible. However, for previous participants who cannot be reached, researchers are not obligated to locate individuals, especially if these activities are out of the scope of the study's research aims and resources.

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Conclusion

During the course of the CKiD Study, the prevailing standards for the protection of participants in genetic research studies have changed with advances in genome sequencing technologies. These allow for less expensive and more informative genomic testing. Paradigms for nondisclosure of research results may no longer reflect the desires of research participants. Investigators need to anticipate and consider their policies about disclosure of results. Pediatric investigators face additional concerns regarding the complex nature of parental permission, child assent, and readdressing consent when the participant reaches the age of majority. At this time, broad input is needed from ethicists, families, participants, and other stakeholders to further develop appropriate policies governing genomic research.

CKiD is planning to conduct research to better understand values and preferences regarding genomic testing and disclosure of individual research results in collaboration with CKiD participants and their parents. The CKiD cohort presents a unique opportunity to study these emerging issues. We are fortunate to have the long-term commitment and engagement of the parents, patients, and researchers involved in this study to further investigate this issue of great importance to the clinical and research communities.

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Box 1.**Opportunities and Challenges of Disclosing Individual Research Results
To Research Institutions/Investigators****Opportunities**

- Supports transparency and potentially enhances public engagement and trust in the research enterprise.
- Honors the role of participants as active partners in the research endeavor.
- May increase enrollment in research endeavor.
- A method of demonstrating respect and gratitude to research participants.
- Disclosure of research results is consistent with models of community-based participatory research.

Challenges

- Institutions and researchers lack the experience and resources to implement procedures and processes for disclosing individual research results.
- Increased concerns regarding liability of investigators and institutions regarding disclosure of individual research results.
- Lack of broad experience and evidence base to guide IRBs and institutions potentially tasked with weighing risks and benefits of results disclosure.
- Results generated by research not intended for clinical care may not be of uncertain significance or may not be analytically or clinically valid.
- Lack of infrastructure to facilitate the disclosure of research results. Results may be set up to be disclosed through the participant's health care provider, but the provider may not have a strong understanding of the test result.
- Few empirical data regarding the actual (vs potential and perceived) risk to participants after individual research results disclosure.
- CLIA prohibits return of results from non-CLIA-certified laboratories.
- Disclosure may undermine certain research designs (eg, single or double blinding).
- Disclosure necessarily requires diversion of resources from the primary goal of research, to generate generalizable knowledge.

To Participants**Opportunities**

- Discovery of clinically actionable results allowing for preventative interventions, treatments, or other actions (including surveillance for early detection).

- Inform decisions for reproductive planning, life planning, and individual-level risk reduction efforts.
- Personal value of research results without need for action (participants learn information about themselves that they would not otherwise obtain: for example, identifying a previously undiagnosed or unknown cause of a health condition, ending the “diagnostic odyssey” and limiting the need for further diagnostic testing and procedures).
- Benefits to the family. Identifying a parent at risk for a hereditary, actionable condition would improve the parent’s health and their ability to support the child.^a

Challenges

- Boundaries between research and clinical care are less clear to participants and foster “therapeutic misconception” and unrealistic expectations of research results.
- Potential for psychological distress with disclosure of results associated with serious health conditions or with uncertain meaning.
- Inappropriate action (due to false positives) or inaction (due to false negatives) due to test results not validated for clinical use. Research test results may be inaccurate, invalid, misleading, or uncertain in clinical significance.
- Unintended social consequences due to stigmatization, economic impact, or disruption of relationships with others (eg, misattributed paternity).
- Concern for potential breach of privacy and exposure to the risk for discrimination.

^aBased on information in Green et al.¹⁶ and Wilfond et al.²¹
Based on information in Brothers et al.⁴⁰

Box 2.**Waiver of Consent and Non–Human Subjects Research in the United States****Criteria for Waiver of Consent:**

1. The research involves no more than minimal risk to the participant(s).
2. The waiver or alteration will not adversely affect the rights and welfare of the participant(s).
3. The research could not be practicably carried out in the absence of the waiver or alteration.
4. When appropriate, the participant will be provided with additional pertinent information after participation.

Criteria for Non–Human Subjects Research:

1. The private information or specimens were not collected specifically for the proposed research through an interaction or intervention with living individuals.
2. The investigator(s) cannot readily ascertain the identities of the individual(s) to whom the coded private information or specimens pertain.

Figure 1.

Flow chart to guide potential disclosure of individual results. Adapted from the Boston Children's Hospital Gene Partnership Informed Cohort Oversight Board, as depicted in Holm et al,³⁴ with permission of Springer Nature. Original flow chart © American College of Medical Genetics and Genomics.

Figure 2.

Disclosure guidelines by participant age. After analytically and clinically valid results are available and reviewed by the designated committee, individual research results are disclosed according to participant preferences by age groups. Adapted from the Boston Children's Hospital Gene Partnership Informed Cohort Oversight Board, as depicted in Holm et al,³⁴ with permission of Springer Nature. Original flow chart © American College of Medical Genetics and Genomics.

Table 1.

Disease Phenotypes and Genes Recommended by ACMG for Disclosure When Present as Secondary Findings

Disease Phenotype	Gene
Onset Typically in Childhood	
Ornithine transcarbamylase deficiency ^a	<i>OTC</i>
Retinoblastoma	<i>RB1</i>
Tuberous sclerosis complex	<i>TSC1, TSC2</i>
WT1-related Wilms tumor	<i>WT1</i>
Catecholaminergic polymorphic ventricular tachycardia ^b	<i>RYR2</i>
Wilson disease	<i>ATP7B</i>
Onset Can Occur in Childhood or Adulthood	
Li-Fraumeni syndrome	<i>TP53</i>
Peutz-Jeghers syndrome	<i>STK11</i>
Familial adenomatous polyposis	<i>APC</i>
Juvenile polyposis	<i>BMPRIA, SMAD4</i>
Von-Hippel-Lindau syndrome	<i>VHL</i>
Multiple endocrine neoplasia type 1	<i>MEN1</i>
Multiple endocrine neoplasia type 2	<i>RET</i>
Familial medullary thyroid cancer	<i>RET</i>
<i>PTEN</i> hamartoma tumor syndrome	<i>PTEN</i>
Hereditary paraganglioma-pheochromocytoma syndrome	<i>SDHD, SDHAF2, SDHC, SDHB</i>
Neurofibromatosis type 2	<i>NF2</i>
Ehlers-Danlos syndrome, vascular type	<i>COL3A1</i>
Marfan syndrome, Loey-Dietz syndromes, and familial thoracic aortic aneurisms and dissections	<i>FBN1, TGFBRI, TGFB2, SMAD3, ACTA2, MYH11</i>
Hypertrophic cardiomyopathy, dilated cardiomyopathy	<i>MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA</i>
Arrhythmogenic right ventricular cardiomyopathy	<i>PKP2, DSP, DSC2, TMEM43, DSG2</i>
Romano-Ward long-QT syndrome types 1, 2, and 3, Brugada syndrome	<i>KCNQ1, KCNH2, SCN5A</i>
Familial hypercholesterolemia	<i>LDLR, APOB, PCSK9</i>
Malignant hyperthermia susceptibility	<i>RYR1, CACNA1S</i>
Onset Typically in Adulthood	
Hereditary breast and ovarian cancer	<i>BRCA1, BRCA2</i>
Lynch syndrome	<i>MLH1, MSH2, MSH6, MPS2</i>
<i>MVH</i> -associated polyposis; adenomas, multiple colorectal, <i>FAP</i> type 2; colorectal adenomatous polyposis, autosomal recessive, with pilomarcinomas	<i>MUTYH</i>

Note: Information obtained from Kalia et al,¹⁸ except where indicated.

Abbreviation: American College of Medical Genetics and Genomics.

^aIn males, occurs in newborns; in females, occurs in children.

^bBased on Behere and Weindling.⁴¹

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