

Pitfalls and Challenges of Consenting to Genetic Research Studies



Hila Milo Rasouly¹ and Maddalena Marasa¹

¹Department of Medicine, Division of Nephrology, Columbia University Medical Center, New York, New York, USA

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As genetics is introduced to all fields in medicine, there is a growing awareness of the dependence of genetics data on clinical information.¹ Longitudinal studies combining deep-phenotyping and genetic testing of diverse populations are required to ensure an evidence-based usage of genetics in medicine, as both comprehensive clinical information and diverse genetic ancestries are crucial to the improvement of genetic variants' interpretation.^{2,3}

Genetic research has enabled the discovery of many genes causing or significantly increasing the risk for kidney diseases and has uncovered the difficulty of clinically diagnosing certain genetic disorders in nephrology.⁴ For example, individuals with incomplete penetrance of Alport syndrome are easily misdiagnosed unless genetic testing is performed. Only large-scale genetic testing of individuals with chronic kidney disease will allow

us to grasp the phenotypic variability of known genetic disorders. In addition, genetics is already used as an eligibility criterion in several clinical trials (Alport syndrome, Dent disease, and Fabry disease are a few examples⁵; see [Supplementary References](#)). As the stratification of cohorts based on genetic markers or mutations has empowered research in other medical fields and has led to new treatments, molecular diagnoses could facilitate the design of clinical trials in nephrology.

It is estimated that up to 10% of adults reaching end-stage renal disease have a Mendelian form of kidney disease. However, even for congenital forms of kidney diseases, the diagnostic rate is reported to be only 10% to 15%.¹ Although new genes causing Mendelian forms of kidney diseases, and new genetic variants predisposing to common forms of kidney diseases, are periodically identified, larger cohorts of well-characterized patients are needed to hasten the rate of discovery.

Although the benefits of genetic research are clear, some ethical concerns also exist, explaining the allocation of research funds to the “ethical, legal and social implications research program” (ELSI) as

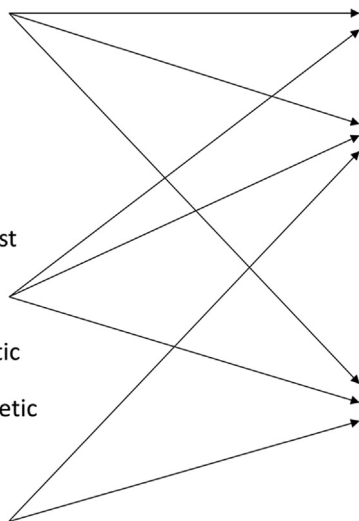
part of the launch of the human genome project. The risk of genetic information misuse has also led many countries to approve laws protecting citizens undergoing genetic testing, such as the Genetic Information Nondiscrimination Act in the United States and the general mandate prohibiting genetic discrimination in the European Union. Nevertheless, not all forms of discrimination based on genetic information are covered by those legal measures. In addition, the controversial use of DNA in the criminal system, and the general distrust of some minorities towards the government, have been reported as preventing minorities from undergoing genetic tests and participating in genetic research,³ highlighting the importance of the informed consent process. The information provided during the consent process is crucial to build and maintain the trust of research participants and to ensure realistic expectations. As some aspects of genetic research are unique, such as the familial implications of the results, as well as the risk factors shared by certain minority groups (i.e., *APOLI*), the specific information that needs to be covered during the informed consent process has been thoroughly discussed and includes an in-depth discussion of risks and benefits.⁶ Although genetic counselors used to consent participants to genetic studies, the spreading of genetic research and the shortage of genetic counselors has constrained most studies to use clinical research coordinators (CRCs) without a formal training in genetics as recruiters for genetic research.

Troost *et al.*⁷ report the recruitment of patients with chronic kidney disease for a genetic biobank as part of C-PROBE (Clinical Phenotyping and Resource

Correspondence: Hila Milo Rasouly, Renal Section, Columbia University Department of Medicine, 1150 Saint Nicholas Avenue, RBP 413, New York, New York 10032-3784, USA. E-mail: hm2673@columbia.edu

Factors affecting consent rate to genetic research

- **Participant-related**
 - Demographics
 - Socioeconomic background
 - Genetic literacy
 - Prior exposure to genetic research/testing
 - Familiarity with the clinical setting
 - Familiarity with the study team
 - Language and cultural barrier/mistrust
- **Site-related**
 - Providers' confidence with genetics
 - Providers' endorsement of the genetic research
 - CRC confidence in consenting to genetic research
 - CRC turnover
- **Protocol-related**
 - Local IRB requirements/policies
 - Option of return of results



Possible tools to promote informed consent to genetic research

- **Participant-related**
 - Patient education tools for genetic research
- **Site-related**
 - Genetics training for providers
 - Providers' commitment to the genetic research
 - Centralized CRC training for genetic research consent process
 - Dedicated CRC to genetic studies
 - Diverse CRC team according to the targeted population
- **Protocol-related**
 - Standardized procedures and policies for informed consent in genetic research

Figure 1. Factors affecting consent to genetic research and possible tools to address them. The factors affecting consent rate are listed on the left, and the possible tools to promote informed consent to genetic research are on the right. The arrows point to the relation between them. CRC, clinical research coordinator; IRB, institutional review board.

BioBank Core), a prospective observational study conducted in 7 sites. A total of 1628 individuals recruited to C-PROBE were also invited to enroll to the genetic biobank. Strikingly, the vast majority (95.5%) of C-PROBE participants consented to the genetic biobank at the first approach, generating a diverse cohort of participants in terms of race, ethnicity, and educational level. This diversity is remarkable given previous reports highlighting the difficulty of recruiting minorities to research.³ In addition, as C-PROBE is a longitudinal study, participants were periodically asked to re-consent to the study as well as to the genetic biobank. This protocol enabled the investigation of the potential demographic, clinical, and socioeconomic factors associated with specific refusal to the genetic biobank, despite consent to the nongenetic components.

The 73 C-PROBE participants who declined consent to the

genetic biobank at the first visit can shed light on the motivations of decliners as well as the potential misunderstandings of individuals who did enroll. Similarly, although only a very small number of participants (50 individuals) changed their consent status over time, information regarding their reasons would be extremely valuable. If a possible reason to decline at the first visit may be lack of time or unwillingness to donate an additional blood sample, the decision to withdraw at the follow-up visit may uncover inconsistencies in the informed consent process, misunderstandings, and potential ethical concerns. Although surveys and qualitative interviews of these participants are desirable to answer those questions, the analysis provided by Troost *et al.*⁷ enables us to uncover some patterns.

The recruitment site was the only factor significantly associated with the enrollment rate both at the first approach and at

follow-up visits. As pointed out by the authors, there are several elements that can have an impact on site recruitment performance (Figure 1). In particular, the CRC experience and confidence in consenting for genetic research can play a key role. Although Troost *et al.*⁷ reported a shared training protocol for their recruiters, the changes in the consent status in low-performing sites, as well as the few questions raised by participants across sites, point to the possible limited discussion about genetic biobanking during the informed consent process. Likewise, the lack of difference in the consent rate of individuals with and without family history of kidney disease may reflect a lack of understanding of the aims of genetic biobanking. From our experience, CRCs who are more familiar with consenting for genetic studies are more likely to engage the potential participants and prompt them to ask questions. A centralized,

professional training for CRCs recruiting for genetic studies is desirable to provide them with skills needed to adequately and uniformly approach potential participants. Similarly, differential provider endorsement for the genetic biobanking could affect a site performance. Genetics trainings for providers may also increase their capacity to discuss the benefits of genetic research with their patients. An additional element potentially affecting the consent rate is participant genetic literacy. Even though Troost *et al.*⁷ did not observe a significant association between education and consent rate, education has been shown to be a poor predictor of genetic literacy. Future studies directly measuring genetic literacy may uncover its association with consent rate, as well as fluctuations in consent status, and prompt the implementation of patient education tools as part of the recruitment for genetic research.

As one of the explicit goals of the genetic biobank is to enroll a diverse population in terms of race and ethnicity, it is important to carefully analyze the impact of self-reported ancestry on consent rate. As reported in previous studies, individuals self-identified as African American had the lowest consent rate (7%) compared to all other groups, and this difference was statistically significant at the first approach. This group also had the highest rate of individuals declining to biobanking at the follow-up visit despite an initial consent. However, the statistical difference based on ancestry disappeared at the follow-up visits. The longitudinal participation in a study and the familiarity with the study team may alleviate factors previously reported as preventing minorities from participating in genetic studies, such as mistrust. Similarly, some studies

have suggested that diverse CRC teams are more effective at recruiting diverse populations. It is worth mentioning that the option for genetic biobanking was part of the broader study consent form and may have increased the consent rate for the genetic component. On the other hand, as the authors do not report the decline rate for the C-PROBE study itself, we do not know whether the reported consent rate is an underestimation of the differential participation rate to research between individuals from different ancestries.

Recruitment efforts like that reported by Troost *et al.*⁷ provide crucial resources for the implementation of genetics in nephrology. This is one of multiple studies collecting longitudinal clinical information and biosamples, including genetic biobanking, from patients with kidney diseases (such as CureGN, CKiD, CRIC, FIND, Neptune, AASK, APOLLO, KPMP).⁸ Although many studies do not offer the return of genetic results to participants, the report recently issued by the National Academies of Sciences, Engineering, and Medicine (NASSEM) encouraged researchers and regulators to return more information to study participants.⁹ Unfortunately, not all those studies have retention mechanisms, thus complicating the re-contact of participants for return of results or collection of additional clinical information needed to refine the interpretation of genetic findings. It would be interesting to see whether the C-PROBE study, as a longitudinal study, will offer the opportunity of return of genetic results in the future. However, the option of returning results introduces an additional level of complexity to the genetic informed consent process thus reinforcing the need of standardized procedures and policies⁹ (Figure 1).

In conclusion, the C-PROBE experience demonstrates that, regardless of demographic and

clinical factors, the vast majority of the patients with kidney diseases are willing to enroll into a genetic biobank. It also points to the potential impact of site-specific factors on the consent rate, thus highlighting the need of standardized procedures for the informed consent in genetic research, including educational tools for both providers and potential participants, as well as centralized training for CRCs enrolling to genetic studies. Finally, studies assessing the impact of return of genetic results on the consent rate and evaluating the participant understanding and perception of genetic research in nephrology would be highly valuable.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary References.

Supplementary material is linked to the online version of the article at www.kireports.org.

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