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RESEARCH PARTICIPANTS' PERSPECTIVES ON GENOTYPE-DRIVEN RESEARCH RECRUITMENT

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Abstract

Genotype-Driven Recruitment is a potentially powerful approach for studying human genetic variation but presents ethical challenges. We conducted in-depth interviews with research participants in six studies where such recruitment occurred. Nearly all responded favorably to the acceptability of recontact for research recruitment, and genotype-driven recruitment was viewed as a positive sign of scientific advancement. Reactions to questions about the disclosure of individual genetic research results varied. Common themes included explaining the purpose of recontact, informing decisions about further participation, reciprocity, "information is valuable," and the possibility of benefit, as well as concerns about undue distress and misunderstanding. Our findings suggest contact about additional research may be least concerning if it involves a known element (e.g., trusted researchers). Also, for genotype-driven recruitment, it may be appropriate to set a lower bar for disclosure of individual results than the clinical utility threshold recommended more generally.

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Identifying and contacting individuals about their interest in research participation must take place within the context of well-established requirements for ethically responsible research (National Commission, 1979). Even so, research recruitment is typically considered to involve fewer risks than research participation. When contacted by a researcher, individuals have several options, including not responding, expressing disinterest at the outset, or learning more about the research and then making an informed decision about whether to take part (Beskow et al., 2004).

However, when genetic information that is generated in one study is used as the basis for identifying and recontacting participants about further research, concerns more commonly associated with *participation* in genetic research are shifted to the *recruitment* phase (Beskow et al., 2010). This kind of "recruitment by genotype" is a potentially powerful new approach for studying the functional significance of human genetic variation (McGuire & McGuire, 2008). Under this approach, investigators use an existing study population for which genetic analyses have been conducted to identify individuals who possess a gene variant of interest. Those individuals are then recontacted to invite their participation in further research involving in-depth phenotyping to better understand the relationship between observable traits and that particular variant (Beskow et al., 2010). Genotype-driven recruitment eliminates the time-consuming and expensive step of screening new populations to find subjects who have the variant of potential significance (Chulada et al., 2008). Such recruitment could be undertaken when investigators want to recontact selected participants in their own studies for further research (Beskow et al., 2010), in the context of biobanks that maintain a link to identifying information (Chulada et al., 2008), and—hypothetically, at least—by searching for individuals who have a particular gene variant across multiple datasets stored in centralized databases, such as dbGaP (McGuire & McGuire, 2008). Genotype-driven recruitment could increase the utility of the massive amounts of data generated in genome-wide association studies, only a tiny fraction of which is related to the disease or condition originally under study (McGuire & McGuire, 2008), and speed progress toward the ultimate goal of benefitting human health.

At the same time, genotype-driven recruitment raises concerns about the use and disclosure of genetic information as part of the offer to participate in research. There is a fundamental tension between avoiding the disclosure of individual genetic research results that may be unwanted and/or unsubstantiated and possibly misleading, and leaving prospective participants uninformed about the purposes of the additional research and why they are eligible to participate (Beskow et al., 2010).

To begin addressing this challenge, we conducted in-depth interviews with research participants involved in studies where genotype-driven recontact occurred. We gathered empirical data on their opinions about such contact, focusing on: (1) the acceptability of recontact for the purposes of research recruitment and (2) whether or not genetic research results from one study should be disclosed during the recruitment process for additional research. These interviews were carried out collaboratively at three sites: Duke University, the University of North Carolina at Chapel Hill, and Seattle Children's Research Institute. This paper reports participants' responses to key interview questions across all sites, including a summary of any between and/or within study variation as well as the qualitative themes that arose in participants' answers. Three other papers in this issue of *JERHRE*—one

from each study site—delve more deeply into particular aspects of that site's data, based primarily on characteristics of the study population that was interviewed (Cadigan et al., 2011; Namey & Beskow, 2011; Tabor et al., 2011).

Methods

Instrument Development

Members of the research team from across the three sites developed an interview guide based on knowledge of the issues and literature concerning research recruitment, informed consent, disclosure of individual genetic research results, human research protections, and qualitative interview methodology. Because our aim was to assess and describe interviewees' perspectives on ethical and policy issues in the emerging area of genotype-driven recruitment, many of our questions were framed to elicit yes/no, positive/negative, or simple rating responses, followed by more open-ended explanations of responses. We revised our guide through iterative rounds of comments from team members, as well as pilot testing with three eligible participants at Duke. The guide (available upon request) shared among the sites included questions focusing on participants' experience and opinions regarding research participation, informed consent, recontact for the purposes of research recruitment, and disclosure of individual and aggregate results in the context of genotype-driven research. Sites made minor modifications to the guide as necessary to accommodate the characteristics of their particular study populations. The guide included a specific definition of "individual genetic research results" to help ensure that participants were commenting on the concept we intended (Box 1).

Data Collection

Across the three sites we interviewed a total of 78 participants who had taken part in a diverse group of six studies where genotype-driven recontact had occurred. These original studies differed in terms of their basic study design and study population (Table 1).

- At Duke, interviews were conducted with individuals diagnosed with epilepsy who participated in a study of the genetics and pharmacogenetics of epilepsy ("Epilepsy"). Following the discovery of large heterozygous deletions in some study participants, the original researchers had carried out genotypedriven recruitment in order to further assess the phenotypic consequences and effects on gene expression of this deletion.
- At UNC, individuals were interviewed from two studies: One was a study of genetic modifiers of cystic fibrosis ("CF"), involving individuals who had been diagnosed with the condition; the second was a population-based registry of healthy volunteers ("Biobank"). These two studies were the sources of phenotypic cases and controls, respectively, for a genotype-driven follow-up study of cystic fibrosis (all eligible participants had the gene variants of interest).
- At Seattle Children's, parents were interviewed from three separate studies involving children and in which genotype-driven recontact occurred: (1) a study called SEARCH for Diabetes in Youth ("Diabetes"), a primary aim of which was to develop approaches to classifying different types of diabetes; (2) the Autism Genetic Research Exchange ("AGRE"), a repository of clinical and genetic information designed to facilitate autism research; and (3) the Study of Autism Genetic Exploration ("SAGE"), the goal of which was to identify genes that affect the development of autism. The latter two studies were combined in this analysis (and referred to as the "Autism" studies). Based on our review of the data, we believe the shared experience of autism was more likely to influence responses to the interview questions presented here than study-specific experiences. Combining

these studies did not significantly change the response distributions for any question except two; for those, we present the results separately.

We included in our interview sample participants who had and had not been recontacted as part of the genotype-driven recruitment that occurred in the original study. A member of the original study team initiated communication with participants, via telephone or letter, to inform them about our interview project. We then gave interested participants additional information and scheduled interviews with those who were eligible. Further details concerning site-based recruitment procedures are provided elsewhere (Cadigan et al., 2011; Namey & Beskow, in press; Tabor et al., 2011).

Interviews at each site were carried out by research team members with training and experience conducting such interviews. Most interviews lasted between 30 and 60 minutes. Whenever possible, interviews took place in person; when an in-person interview was not possible, the interview was conducted by telephone. The relatively structured format of our interview questions was intended to limit potential bias due to differences between in-person and telephone interviews, as well as cross-site differences in how questions were asked. With participants' permission, interviews were audio-recorded and later professionally transcribed for purposes of analysis. Participants provided verbal consent at the time of the interview and were offered $40 compensation for their time.

The Institutional Review Board (IRB) at Duke University determined that the research was exempt under 45 C.F.R. 46.101[b][2] and served as the IRB of record for the University of North Carolina at Chapel Hill; Seattle Children's IRB also determined this study to be exempt.

Data Analysis

All interview transcripts were uploaded into NVivo 8 (QSR International 2008), and a structural codebook was devised and shared among the sites. ("Structural code" refers to question-based, rather than theme-based, codes [MacQueen et al., 1998].) Each site applied structural codes to their own transcripts to facilitate question-based analysis across sites. Once all structural coding was completed, the sites' NVivo files were merged into a single cross-site file, from which the analyses presented here were carried out. Though inter-coder reliability is less of a concern with structural coding (given that questions and responses are captured without regard to their thematic content), we ran code frequencies to confirm that all questions/responses had been coded in each transcript.

Using the cross-site dataset, two coders (E.E.N and L.M.B.) working sequentially reviewed the structural codes identified for inclusion in this analysis and performed a second round of coding to characterize participants' responses. We present here a description of the approximate proportion of interviewees who gave different responses to each question and of the variation in responses between and within the six participant groups. Due to nonrandom sampling and small, uneven sample sizes, these proportions and variations should not be interpreted as generalizable; rather, we are capitalizing on the structured nature of our interview guide to facilitate clear communication about multiplex data gathered from this particular group of interviewees. This approach also enables comparison of responses between questions and a framework for interpreting the richer thematic data. With regard to thematic variation, narrative segments presented here are exemplary of frequently mentioned ideas, unless stated otherwise.

Results

Participant Characteristics

The characteristics of our interviewees were a function of the original studies from which they were recruited. Approximately two-thirds were female, and most were white, non-Hispanic, and college educated (Table 2). Half had been recontacted about taking part in a genotype-driven follow-up study (a result that follows from our purposive sampling to interview some individuals who had been recontacted and some who had not).

Views about the Acceptability of Recontact for Genetic Research Recruitment

We asked a series of questions to ascertain interviewees' opinions about recontact—not necessarily genotype-driven—for the purposes of further research recruitment. Responses were consistently positive across all of the studies to our baseline question, "Generally speaking, if you're in one study do you think it's all right for researchers to contact you about being in another study?" (Table 3). Overall, a substantial majority (> 85%) of interviewees said "yes". Many expressed a positive attitude toward research in general, including themes of altruism as well as supporting the goals of research. Several recognized recontact as an efficient way to facilitate research, particularly given that, when contacted, one could decline further participation. Others suggested that willingness to participate in one study was a likely indicator of willingness to participate in additional research, particularly when the burden involved is low.

The primary concern cited with regard to recontact was privacy. Only one person across all of the studies expressed a directly negative view, although several of those whose personal opinion was positive anticipated that other people might have issues with privacy or be distressed by recontact itself.

CONSENT FORM DISCLOSURES AND OPTIONS CONCERNING RECONTACT ABOUT ADDITIONAL RESEARCH—Opinions were mixed with regard to the importance of being informed ahead of time about the possibility of future research contact. When asked to rate "How important would it be to you personally to know right up front that researchers might contact you about more research in the future?" (Table 4), a majority of Diabetes interviewees said it would be important. This was also the most common answer among CF, Epilepsy, and Autism-AGRE interviewees, but was expressed by less than half —reflecting the diversity of opinion within these studies. Biobank and Autism-SAGE interviewees generally assigned less importance to being informed about the possibility of recontact.

Many of those who said it would be important to know that recontact could occur indicated that it was simply a good idea to give people advance notice. Some went further in suggesting that it might factor into their decision about taking part in the initial study. Several highlighted the potentially substantial time lag before recontact might occur as the reason it would be important to know about the prospect early on. Some noted that unexpected recontact could cause concerns about whether their confidentiality had been breached.

Among interviewees who said being informed about the possibility of future research contact was not important, some said it was not necessary because recontact itself was acceptable. Several acknowledged that researchers may not know ahead of time that they would later want to recontact participants.

Of the interviewees who said it would be important to be informed about such contact in advance (n = 35), more than two-thirds said it would be important to have a *choice* at the

time of initial consent about whether researchers could contact them about more research in the future. Several interviewees noted that having a choice was important, even for participants favorably inclined toward additional research, but especially so for those who might want to take part in one study without being required to agree to future contact.

Interviewees who said it was not important to have a choice about recontact frequently recognized that, if recontacted, they would still have a choice about whether to actually participate in a subsequent study. One person linked his opinion that choice was not important to a problem with the growing complexity of consent forms:

> When you start adding in a lot of options and fine print, then it seems like homework reading over it, and that will discourage someone like myself that tends to be more laid back… I can see where more knowledge would be helpful, but at the same point, too much knowledge would be a turnoff. (Biobank-C22)

POTENTIAL MODIFIERS OF VIEWS ABOUT THE ACCEPTA BILITY OF RECONTACT FOR RESEARCH RECRUITMENT—We asked about several factors that might modify participants' views about the acceptability of recontact for the purposes of research recruitment. Excluding Biobank interviewees (who had consented to participate in a biorepository that a variety of researchers could access), responses were consistently positive across all of the studies to our question, "How would you feel if you were contacted about taking part in more [original condition] research, but the new study was being conducted by researchers other than [original researchers]?" Overall, a substantial majority (> 75%) indicated they were amenable to contact by new researchers.

Among those who indicated willingness to be contacted by new researchers (n = 49), most said it would not matter whether the new researchers were also from the original institution. Interviewees' responses to both of these questions—about contact by different researchers or by researchers from a different institution—generally reflected a positive view of research and trust in the researchers and institutions known to them, which they often extended to other major academic medical centers.

Finally, reactions were mixed when we asked "How would you feel if you were contacted about taking part in more genetic research, but the new study was not about [original condition]?" (Table 5). A majority of Epilepsy, Autism-SAGE, and Diabetes interviewees responded positively. CF and Autism-AGRE interviewees most commonly responded negatively, although opinions were diverse and none of the responses were expressed by a majority. (We did not ask Biobank interviewees this question because they were recruited from the general population, not based on having been diagnosed with a particular condition.)

Among those who felt positively about taking part in research on other conditions, several expressed general altruism or a desire to contribute to research on a condition affecting their family or someone they know. Many of those who responded negatively described a preference to focus their energies on furthering scientific knowledge about their own condition.

ACCEPTABILITY OF GENOTYPE-DRIVEN RECONTACT FOR RESEARCH RECRUITMENT—With regard to the acceptability of genotype-driven recontact in particular, responses were consistently positive across all of the studies to our question "How would you feel if the reason researchers wanted to contact you about being in a new study was because of something they learned about your DNA in the first study?" (Table 6). Overall, a substantial majority of interviewees (> 85%) responded favorably. Many felt such contact would be expected or a welcome sign of scientific advancement. The opportunity to

facilitate more research, including the perception of genetics as an important area of research, was another frequent theme.

Interviewees frequently answered our question about the acceptability of genotype-driven recontact by stating that they would want to know what researchers had learned. Some felt that learning their results could influence their decision about taking part in the next study. One person questioned the ethics of researchers *not* letting participants know what they had learned:

> But would that be ethical for a researcher to find something that they're interested in studying further pertaining to my family's DNA and then call back and ask questions relevant to that without letting me know, without giving me that information? Would that be ethical research? (Autism, AGRE-S13)

No interviewee expressed a decidedly negative opinion about genotype-driven recruitment, although some noted a few reservations—including concerns about having advance notice, maintaining confidentiality, and the potentially distressing nature of the information.

Excluding SAGE participants (who had consented to a study where genotype-driven follow-up was an integral component), most interviewees said it would have had little or no effect on their decision to take part in the original study if they had known ahead of time that they might be contacted about additional research based on something researchers had learned about their DNA. Among those who said such knowledge would have had a big effect on their decision, nearly all said the impact would be positive:

> If they say "If you take part in this study, and we contact you as a sort of a follow-up because we've detected something," then to me that's a positive… Because you're actually looking at something that could actually help benefit in some cases. (CF-C13)

Disclosure of Research Results in the Context of Genotype-Driven Recontact

When asked, "In your opinion, when a researcher contacts people about being in a new study, should she generally offer them their individual genetic research results from the first study or not?" (Table 7), a large majority—ranging from approximately 60% of Epilepsy and Diabetes interviewees to over 85% of CF and Autism interviewees—said researchers should offer individual results. In contrast, opinions among Biobank participants were considerably less favorable, with only about one-fourth saying results should be offered and most expressing an uncertain or "other" response.

Among interviewees who said results *should* be offered in the context of genotype-driven recruitment, many felt it would be important to explain the purpose of recontact, and some further thought the information would be important for informing the person's decision about taking part in additional research. Another common reason given was the opportunity to educate and empower patients. Although some felt that the information would be valuable in and of itself, others seemed to assume it would convey medical or personal benefit. Some suggested that researchers should offer results as a matter of reciprocity, i.e., receiving information was a fair exchange for their contribution to the research. Finally, several answered this question by stating their personal desire to receive individual results, but explicitly noted that others might feel differently:

> Some people prefer more information and other people get scared of more information, so by leaving it up to the person to decide whether or not they want that, I would think would be the best way to do it. I'm a curious person so I'd like to get tons of information; other people find it alarming or whatever and may not want it. (Diabetes-S16)

Interviewees who said researchers should *not* offer people their individual genetic results when contacting them about additional research primarily cited concerns about causing unnecessary worry or distress. Those who did not reach a conclusion about whether researchers should offer individual results commonly expressed uncertainty about the best course of action, or said "it depends" on factors such as whether the information was beneficial, and whether participants had been told in advance about such disclosure.

THE IMPORTANCE OF CLINICAL VALIDITY—When we raised the possibility that results disclosed in the process of genotype-driven recruitment could have uncertain validity, opinions were mixed but generally less favorable compared to our baseline question about the disclosure of results. When asked "What if researchers find a change in a gene that might be related to the disease they are studying, but they are not sure if it is or what it means?" (Table 8), a majority of CF and Autism interviewees said such results should be offered. This was also the most common response among Diabetes interviewees, although it was expressed by less than half. In contrast, the view that such results should not be offered was the most common response in the remaining two studies, expressed by a majority of Biobank interviewees and many Epilepsy interviewees.

In several instances, those who said researchers *should* offer results even when clinical validity was uncertain referred to the recruitment context and the importance of explaining why they were being contacted. The beliefs that "information is good" and that people have a right to information about themselves were other common themes, along with the potential for taking personal responsibility to seek out other sources of information to help clarify uncertain results.

The most common justification for why researchers should *not* offer uncertain results was to avoid causing undue worry, particularly when there was no corresponding benefit. One person noted the possibility of both undue worry and unfounded hope:

> Um, boy, that's hard, you know… I think that's something, an ethical issue for you guys, because you don't want people to have false hope or false panic, and especially if you don't know what it means… I'm not sure they should do that. (Autism, AGRE-S11)

Others commented that uncertain results did not constitute "information," or that they could cause misunderstanding or confusion.

THE IMPORTANCE OF CLINICAL UTILITY—When we asked about the disclosure of results with uncertain utility during the process of genotype-driven recruitment (Table 9), opinions were generally more favorable compared to the possibility of uncertain validity. Most interviewees said researchers should offer results if they "find a change in a gene that they are pretty sure is related to the disease they are studying, but there is no treatment or anything different the person could do based on that information." A majority of Biobank, Epilepsy, and Autism interviewees expressed this view; this was also the most common response among CF and Diabetes interviewees, although it was expressed by less than half.

Among those who said such results *should* be offered, the conviction that any information is valuable was once again a common theme—sometimes described together with the belief that individual results could provide "answers" even in the absence of clinical utility. Interviewees also frequently mentioned the future development of medical interventions and having the opportunity to seek those out. Some participants foresaw the possibility of more immediate benefits, for example in terms of health-related behaviors, reproductive decision making, or life planning. One person seemed to suggest that, in the context of genotype-driven recruitment, researchers would need to think about their current obligations in light of

potential future discoveries, i.e., even if the current result does not merit disclosure, the next one might:

> I think that when they find out the next result they'll be able to say, "You didn't tell me this was going on in the beginning." So a person would be deceived. (Epilepsy-D22)

Interviewees who said researchers should *not* offer results that lack clinical utility cited familiar concerns about causing undue worry with little or no possibility of benefit, problems with understanding, and continuing uncertainty.

THE ROLE OF AGGREGATE RESULTS—Responses across all of the studies were consistently positive with regard to the receipt of aggregate research results in the context of genotype-driven recruitment. Overall, nearly three-fourths of interviewees said it would be important when asked, "How important would it be to you to find out what researchers learned about the role of genes in [original condition] in general, even if you did not get your individual genetic research results?" (Table 10). Many felt invested in the research and wanted to know the outcome of their contribution. Many also thought that having access to aggregate results was an important way to stay updated about the state of scientific knowledge. Others perceived benefit in receiving the aggregate results of genetic research, including being able to provide information to family members who might be affected or finding "answers" as to the cause of their medical condition. One interviewee's comment suggested that the provision of aggregate research results may have implications for health care providers:

> I would probably just take it and, even though I didn't know my individual, I would probably try … to talk with my doctor and see if we can, you know, kind of figure out how he thought I was and … see how he thought as far as looking back at my chart and seeing where things were… And then … when I have kids or when I have a family like I would have that. And like if something ever did happen I'd be like, "Hey, this was definitely me." (Epilepsy-D21)

Discussion

Genotype-driven recruitment is an emerging approach to genomic research that poses ethical challenges stemming from the use and possible disclosure of genetic research results as part of the offer to participate in additional research. The concerns are exacerbated by the uncertain nature of most genetic results: further research is needed specifically because more must be learned to understand their meaning in terms of risk, inheritance, diagnosis, prognosis, and treatment (Beskow et al., 2010). Genotype-driven recruitment will become an increasingly important tool as scientists seek to better understand the function of the human genome by recruiting individuals already known to have particular variants for in-depth phenotyping.

To begin informing the development of policies that both protect participants and facilitate beneficial research, we conducted in-depth interviews with participants in genomic research where genotype-driven recontact occurred. Our interviewees were drawn from six studies that differed in terms of basic study design and study population, thus offering the opportunity to glean a rich array of perspectives.

Given this diversity, it is particularly striking how consistent our interviewees' responses were to certain questions— both within and between studies. Nearly all responded favorably to the general acceptability of recontact for the purposes of research recruitment. These responses were commonly accompanied by statements of altruism and a positive attitude

toward research in general—perhaps reflective of the attitudes that might be expected among many of those who would be candidates for genotype-driven recruitment, i.e., people who have already agreed to participate in at least one research study. Genotype-driven recruitment was viewed especially positively as a sign of scientific advancement and an opportunity to take part in a promising area of research. A substantial majority of our interviewees were amenable to contact about studies conducted by researchers other than those who conducted the original study, perhaps again reflecting support for and trust in the research enterprise among those who have already agreed to participate in research. Across all studies, there was significant interest in receiving information about aggregate research results, oftentimes for reasons related to reciprocity and staying updated on research progress.

For several of our key questions, however, interviewees' responses varied both within and between studies. Although many deemed it important to be informed up front whenever possible about the potential for future research contact and to have a choice about such contact, others felt that having a choice about actually *participating* in future research was sufficient. Similarly, many were amenable to taking part in research on other medical conditions, but others expressed a preference to help with research on conditions affecting them or their family and friends. Factors related to study design and study population could help explain these findings. For example, participants in studies that are otherwise perceived as one-time, circumscribed events (e.g., Epilepsy) may assign more importance to being notified about the possibility for future contact as compared to studies where the ongoing nature is an integral aspect (e.g., Biobank). Populations that are frequently recruited for research (e.g., CF patients) may assign less importance to being notified about possible recontact if they are already accustomed to being approached frequently. Such populations may, however, feel less able to also contribute time and energy to research on conditions other than their own. Study populations defined by having multiple affected family members (e.g., Autism-AGRE) may feel similarly constrained with regard to research on other conditions, and also rate advance notice about future research contact more highly.

Reactions to our questions about the disclosure of individual genetic research results in particular tended to vary within and/or between studies. Common themes across all of these questions included explaining the purpose of recontact, informing decisions about participation in further research, reciprocity, "information is valuable," and the possibility of medical or personal benefit, as well as competing concerns about undue worry, distress, misunderstanding, and confusion. Specifically with regard to our general question about whether researchers should disclose individual results from the first study during the recruitment process for further research, the majority of interviewees in five of the studies said "yes", but those in the sixth study—the Environmental Polymorphisms Registry, a population-based biobank of healthy volunteers—had more reservations. This finding points to a potentially significant explanatory factor, which is that *patients*, i.e., people who have been diagnosed with the condition under study or parents of children with the condition, may likely perceive the risks and benefits of receiving individual genetic results very differently than those who have not been diagnosed with the condition (Cadigan et al., 2011; Namey & Beskow, 2011; Tabor et al., 2011).

Responses were more mixed and less favorable to our question about disclosure of research results that lacked clinical validity. Although many of our interviewees were receptive to uncertain information as long as the uncertainty was clearly explained, our results suggest that not all people diagnosed with the condition under study will find net benefit in information that is ambiguous with regard to informing their understanding of their illness. Likewise, healthy volunteers recruited as controls are unlikely to view unsubstantiated information about a condition they do not have as beneficial, particularly if there is

uncertainty about the meaning of the information for their future risk of that condition. Overall, our interviewees seemed generally less concerned about individual results lacking clinical utility, often based on the expectation that such results would still provide information or answers about their illness (for people diagnosed with the condition), or the expectation that there could still be personal utility as well as hope for future interventions (both for people with and without the condition). Indeed, a potentially concerning facet of our findings is the extent to which our interviewees assumed that genetic research results would convey information serious and certain enough that they would base reproductive or life-planning decisions on it.

As noted in the Methods section, the interpretation of all of our findings is subject to a number of limitations. Within the time and resource constraints of our research, we were only able to interview a small number of participants in each of the original studies and these were not randomly sampled. In addition, most of our interviewees were white and many were highly educated, characteristics that followed from the composition of the original studies from which they were recruited. It is therefore critical to note that our findings cannot be considered generalizable. We described the approximate proportions of interviewees who gave different responses in order to facilitate the clear communication of our data across multiple dimensions, but these proportions apply only to our particular study sample.

Notwithstanding these limitations, our findings represent what we believe are the first data from research participants about genotype-driven recruitment. We carried out in-depth interviews and thus were able to gather important and nuanced insights into participants' range of experiences and opinions, providing a strong foundation for future research.

Best Practices

Data on the opinions and preferences of research participants (as well as other stakeholder groups) are essential for informing policy development on ethical approaches to genotype-driven research recruitment. Although our data are provisional and subject to limitations, they point toward several potential future practices.

First, informed consent disclosures about the possibility of recontact for the purpose of further research recruitment is likely good research practice and may help mitigate ethical concerns related to protecting research participants from unwelcome researcher contact (Beskow, Namey et al., in press).

Second, our interviewees' input suggests that contact about future research may be least concerning if it involves a known or trusted element, e.g., the same researcher, a well-regarded academic institution, the same medical condition.

Third, in the context of genotype-driven recruitment, it may be appropriate to set a lower threshold for return of individual genetic research results than that typically recommended for return of results more generally. For example, although clinical utility is commonly considered an important factor in the decision to offer individual research results (Bookman et al., 2006; Fabsitz et al., 2010; NBAC, 1999), this is a threshold that may rarely be met in the context of genotype-driven recruitment. Findings from our interviews suggest that setting a lower bar for disclosure may be important for avoiding evasion when explaining to prospective participants the purposes of the additional research and why they are eligible, and for promoting informed decision making about further research participation. These reasons for offering results are fundamentally different than those suggested by studies of participant preferences in other contexts, where individual genetic research results were desired because of anticipated personal or health-related benefit (Beskow & Smolek, 2009;

Kaufman et al., 2008; Meulenkamp et al., 2010; Murphy et al., 2008; Ormond et al., 2009; Wendler & Emanuel, 2002).

Finally, our results suggest that factors related to study design and study population may have an important impact on prospective participants' reactions to genotype-driven recruitment and the disclosure of individual genetic research results. Thus, there is unlikely to be a one-size-fitsall approach to genotype-driven recruitment, but rather several approaches that are acceptable when tailored based on careful consideration of contextual factors and informed by empirical evidence whenever possible.

Research Agenda

A strength of our study was the diverse group of original studies from which we recruited interviewees, allowing us to identify a range of perspectives on this emerging topic. In companion papers (Cadigan et al., 2011; Namey & Beskow, 2011; Tabor et al., 2011), we offer more detailed examinations of these different views. However, our sample size was too small for further meaningful stratified analyses (e.g., by demographic factors), which would be a fruitful area for future research.

Another strength of our study was that we obtained detailed responses from participants in genomic research to a series of questions about the return of individual genetic results. Participants' (or hypothetical participants') basic interest in receiving such results has been well documented, but more nuanced exploration of their understanding and preferences—including issues of validity and utility—has been limited. Further research is warranted on this important topic.

The role of aggregate research results also deserves more attention. The provision of aggregate results could be a pivotal step in the process of genotype-driven recruitment, and also serve an important function in terms of satisfying participants' desire to stay updated, find answers as to potential causes of their condition, and to receive something in exchange for their participation (Beskow, Burke et al., in press).

More generally, further research on genotype-driven recruitment should build on our findings and be implemented in studies ideally involving larger sample sizes and the opportunity to gather data from participants prospectively, i.e., before and during the process of genotype-driven recruitment, rather than after it has occurred. It will be vital to assess how participants react to the receipt of genetic information (see, e.g., Green et al., 2009) and what they do with that information. Data from other stakeholders, including researchers, physicians, and IRB chairs (Beskow, Namey et al., in press) is critical to the development of balanced approaches to genotype-driven recruitment.

Educational Implications

When planning genomic research, it is important that research teams and IRBs be aware of the possible future desire to conduct genotype-driven recruitment and of the ethical dilemmas it entails. In particular, they should think about the range of opinions, assumptions, and expectations— as well as potential misunderstandings—that may be held by prospective participants. Whenever possible, it would be beneficial to take steps during the initial study design phase to educate themselves about their particular study populations and to tailor their plans and consent disclosures accordingly. They must also be prepared to communicate clearly with participants about the state of genomic science in their area of research: what is known and not known about the role of genomic factors and the next steps in the research process.

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Box 1. Interview guide definition of "individual genetic research results"

Sometimes when people are contacted about taking part in another study, they are given some individual genetic results from the first study. For example, they might be told what researchers had learned about their genes or DNA. Sometimes they are not given any individual information back.

People think of a lot of different things when they hear "genetic results." For the next several questions, we're going to be talking about something quite specific that I will call "individual genetic research results." Let me explain [READ THE FOLLOWING ALOUD]:

> Researchers doing a genetic study are usually trying to find out whether there is a link between a genetic trait and the medical condition they are studying. By looking at the DNA from everyone in the study, researchers are sometimes able find such a trait. Some people in the study have that particular trait and some people don't. Also, researchers sometimes know something about that genetic trait and what it might mean—but often they are not sure what it means or if it is even related to the medical condition until they do more studies.

So, when I say, "individual genetic research results," I mean information about whether or not you have the genetic trait that researchers identified in their study. Does that make sense to you? Do you have any questions about this definition?

TABLE 1

Original Study Characteristics.

DUKE UNIVERSITY			
Title of original study	Genetics and Pharmacogenetics of Epilepsy (“Epilepsy”)		
Subjects	975 adults with epilepsy		
Recontact for additional research described in consent form?	Yes		
Options offered in consent form concerning recontact?	No		
Consent form disclosures about results	Participants will not receive research results, but will be offered “incidental findings”		
Consent form options about results	None		
Method of recontact	Letter, then phone call		
Individual results provided during recontact?	No		
UNIVERSITY OF NORTH CAROLINA-CHAPEL HILL			
Title of original study	Gene Modifiers in Cystic Fibrosis (“CF”)	Environmental Polymorphisms Registry (“Biobank”)	
Subjects	1,306 adults and children with CF	15,000 adult “healthy volunteers”	
Recontact for additional research described in consent form?	No	Yes	
Options offered in consent form concerning recontact?	No	No	
Consent form disclosures about results	Participants may receive results of “potential clinical consequence”	Participants will not receive results; may or may not receive results in follow-up studies	
Consent form options about results	Participants can opt to receive results of “potential clinical consequence”	None	
Method of recontact	In person, in the clinic	Letter	
Individual results provided during recontact?	No, but told they have one of two genetic variants that may affect severity of CF	No, but told they have one of two genetic variants under study and there is no known relationship between these variants and any disease in people who do not have CF	
SEATTLE CHILDREN’S			
Title of original study	Autism Genetic Resource Exchange (“AGRE”) *	Study of Autism Genetics Exploration (“SAGE”) *	SEARCH for Diabetes in Youth (“Diabetes”)
Subjects	1,163 families with >1 child with autism	1,000 children (with autism or suspected ASD) and their parents	3,474 children with diabetes
Recontact for additional research described in consent form?	No	Yes	Yes
Options offered in consent form concerning recontact?	Yes	No, because recontact was part of the study design	Yes
Consent form disclosures about results	Participants will not receive results	Parents will be told if child has gene variation being studied. No other results given	Results may be given to diabetes provider
Consent form options about results	Option for return of specific test results (Fragile X	None	Participants can opt for their provider to receive results

DUKE UNIVERSITY			
	testing and chromosomal analysis)		
Method of recontact	Phone call	Letter, then phone call	Letter
Individual results provided during recontact?	No	Yes, told that CNV was identified and referred to medical genetics clinic	Yes, preliminary results

* SAGE and AGRE were combined in this analysis as the “Autism” studies; see Methods section for more details.

TABLE 2

Interview Participant Characteristics (n = 78).

	n	%*
Age: Mean = 43; range = 21–67		
Education		
High school	13	17
Associate's degree	3	4
Some college	6	8
Bachelor's degree	37	47
Graduate degree	18	23
Sex		
Female	50	64
Male	28	36
Race		
White	67	86
Black	8	10
Other	3	4
Hispanic	2	3
Original study		
Gene Modifiers in Cystic Fibrosis (CF)	9	12
Environmental Polymorphisms Registry (Milbank)	15	19
Genetics and Pharmacogenetics of Epilepsy (Epilepsy)	29	37
Autism Genetic Resource Exchange (AGRE)	13	17
Study of Autism Genetics Exploration (SAGE)	5	6
SEARCH for Diabetes in Youth (Diabetes)	7	9
Recontacted about follow-up study	39	50

*May not sum to 100% due to missing data.

TABLE 3

"Generally speaking, if you're in one study do you think it's all right for researchers to contact you about being in another study?"

Response	Theme	Examples
Yes	Positive attitude toward research, altruism	• Because I think that it will help others, by getting more information as you go … you want to find out one answer, then you keep working to find more answers. (Epilepsy-D03) • I guess I figure anything that will help… figure out what gene it's on or figure out, you know, like what gives kids a predisposition to get it or whatever, I'm happy to do whatever I can to figure it out. (Autism, AGRE-S02)
	Efficient way to facilitate research	• Yeah, I think it's all right for them to contact you because … there's not a large pool of people with those characteristics… [T]hey already got the names and contact numbers … it's easier to do that than go out to the community and recruit new people and try to sift through those names and stuff. So just reasonable to assume that's how that would be done. (Autism, AGRE-S06) • If you don't contact people … that have the problem, and ask or at least offer to do studies, then you can't advance anywhere with it. So the worst they can do is say no. I don't see any problem with that. (Epilepsy-D14)
	Inclination to participate	• I think that if I was able to agree to do one, to be open to that … I don't see a reason why I should have a concern to do another one. (Epilepsy-D15)
	Minimal burden	• Well, I mean, it's just really not a whole lot to it, so I don't see where it's that big a deal … whether you're in two or three or one. I mean it's not that hard to do. (Epilepsy-D12)
No	Privacy	• Well, I don't know. I mean, I just thought that was a one-time deal… So, that's really the only reason why I did it. I didn't think it was going to be a continuous string of them (Epilepsy-D09). • I could see how maybe some people would feel like their privacy might have been violated… It wouldn't bother me, but it may bother others. I could see how other people might not be happy about that. (Diabetes-S08)
	Distress	• I could see how somebody could perceive it—you know, be concerned or could raise alarms like "You know I was contacted because something was wrong." (Biobank-C07)

TABLE 4

"How important would it be to you personally to know right up front that researchers might contact you about more research in the future?"

Response	Theme	Examples
Important	Advance notice	• When you go and you participate in a study … unless it's made explicitly clear, you kind of assume that it's … open and closes when you leave… It'd be nice to have a heads up that you could be contacted again in the future. (Biobank-C07)
	Inform participation decision	• I think that's kind of a "duh" question, frankly (laughs). I mean … maybe I'm wrong, but most people want to know as much as they could about what their participation might look like. (Autism, AGRE-S11)
		• That would be good to know. It would because it would … make you kind of think "Do I really want to be in this study if it's gonna have some impact on my future?" (Biobank-C12)
	Time lag before recontact	• At least it plants maybe a seed in your mind that you know you're signing up for something longer term than just a 15-minute blood draw. (Biobank-C08)
		• Even if I get a letter and it's two, three years later, at least I know. I like to be a little bit prepared. (Epilepsy-D25)
	Confidentiality	• I mean, you would just like to know that if you are going to do something one time, that you know your information would be … kept confidential and secure, and if you were contacted again when you were told that it was a one-time thing, you would think that maybe your information was compromised. (Biobank-C20)
Not important	Recontact itself is okay	• It wouldn't be important to me, because… I think that's an okay thing to do. If somebody contacted me for a second study, I wouldn't feel like I had been misled somehow, because I didn't know that they might do that. (Autism, AGRE-S01)
	Researchers may not anticipate recontact	• If that is the intent, fine. I don't think that would make a difference to sign up for the first study. If that's not known ahead of time, then you can't tell the person. (Biobank-C19)

TABLE 5

"How would you feel if you were contacted about taking part in more genetic research, but the new study was not about [original condition]?"

Response	Theme	Examples
Positive	Affected friend or family member	• Well I probably got the gene for breast cancer 'cause my mom died of that, my grandma, my aunt. So I probably got that gene too. So if they can cause me not to have breast cancer, that'd be good. (Epilepsy-D13) • Autism is not the only thing that needs fixed. There's other things that are just as important, like heart disease or … a predisposition to cancer, diabetes, any of those things. I mean, if it was for something like Huntington's disease, I probably wouldn't see any possible reason why I should participate since nobody in my family has ever had it. But if it was something that affected our family, personally… (Autism, AGRE-S01)
Negative	Focus on own condition	• I think I would stick to the epilepsy. The epilepsy is what's involving me, it's what I'm looking to know more about. I would stay with the epilepsy. (Epilepsy-D29) • I want to help somebody that's got the same problem I got, you know. (CF-C16)

TABLE 6

"How would you feel if the reason researchers wanted to contact you about being in a new study was because of something they learned about your DNA in the first study?"

Response	Theme	Examples
Positive	Sign of scientific advancement	• I think that'd be great … you would know that the other study worked. (CF-C16) • That's fine. I mean, DNA, that sounds like it could be moving, progressing somewhere. Yeah, that would be good. (Epilepsy-D06) • I would be very happy about that. I mean I would say, "Yay, I'm helping make a difference finding something." (Autism, SAGE-S23)
	Facilitate more research	• It's always good to learn new things about genetics and DNA. So I think it'd be great to learn new stuff and do more research based on what's been learned. That's the whole point of doing research. (CF-C17) • Oh, I'm fine with that … if they found, let's say, we have a predisposition to autism on gene chromosome number 8 or whatever, I'd be fine like if they took all the people they thought that had this … and did another study. I think that's great. (Autism, AGRE-S02)
Positive, would want results	Would want to know what researchers had learned	• If there was something they learned about my DNA, and they want to look into it further, I would understand the value of that. I would have no problems with that. I mean for obvious reasons I might be a little anxious if there was something that they found out. I would want to know what it is. (Biobank-C11) • That would be fine, although I'd wanna know probably what they see that makes them want to look at my DNA. (Epilepsy-D05)
	Inform participation decision	• I'd be willing if it's something that was in my DNA the first time or genetics, it's good for me to be informed of that and that's why I would be willing to further the study. (Epilepsy-D17)
Positive, with some reservations	Advance notice	• Being up front in the beginning is the key to it. If I agree to something ahead of time, I know they're doing it. If I assume that I'm an anonymous donor, and then later on I find out I'm not, then I feel betrayed I guess is the right term for it. (Biobank-C10)
	Confidentiality	• I guess it would depend on if they were a part of the study that they had learned that from. Like if they were just kind of a third party researcher and they learned it through like friends or like seeing the results or whatever it would be a little bit more worrisome for me. (Diabetes-S19)
	Nature of the information	• I think I would feel totally fine with that—unless like the topics of the study or whatever they found was something alarming. (Biobank-C04)

TABLE 7

"when a researcher contacts people about being in a new study, should she generally offer them their individual genetic research results from the first study or not?"

Response	Theme	Examples
Should offer	Explain purpose of recontact	• I think people have a right to know, if they're going to participate in a new study, why. (Epilepsy-D04)
	Inform participation decision	• I think they should. I think that makes a person more wanting to do the research if it's something they found. Otherwise it puts them in the dark, "Why am I doing this again?" (Autism, AGRE-S07)
	Educate/empower patients	• I think any time you have an opportunity to educate a person about CF, particularly if they have it, you should try to do so. I just think that we, in order to be independent and for survival … I like to know what's going on with my body and, you know, what my results are. (CF-C01)
	Medical/personal benefit	• I just think it's important for people to know. I mean for me … if there's gonna be a new drug to market or something that's gonna be beneficial, to me that's something that I'd want to know. (CF-C13) • It's interesting and it would help to kind of clarify things a little bit for me. I mean, I don't know why I have epilepsy. I can't really tie it to anything in particular, so for me it would be great to be able to go, "Oh … it's all so clear now." (Epilepsy-D19)
	Reciprocity	• Yeah, 'cause that's their blood. They have a right to know what's going on. If I sat down and … willingly gave somebody some of my blood for a test, I think I should get it back. I should know the grade of my test since I took it. (Epilepsy-D09)
Should not offer	Undue worry, distress	• The science is too new I think… I don't know that it might—it might cause more worry than necessary. (Biobank-C08) • It depends on whether it's bad or could be interpreted as bad. It's hard to say. You have to be careful about handing out information to people, especially genetic stuff 'cause these days it's the hot topic and "Oh they know this about my DNA," and "What does it mean? What does it mean?" I think it's probably best to not say. (Epilepsy-D16)
Uncertain	Unsure	• I don't know. I'm not really sure on that one. I guess you could go either way because … if everyone wants to know how their results turned out, you know, that could be costly and not really … time effective and all that. (Diabetes-S19)
Other	It depends	• I would say—well, only if it falls into that "I really know for sure this matters in your life" category. I think only if there's concrete knowledge that you can work with should you tell people. Because this is like you know false positives on tests. All it does is freak people out for no reason. And people waste their lives and all their energy and effort chasing something that's not real and is stupid. (Biobank-C09) • It depends on whether or not the participant agrees to that up front and whether the researcher discloses that up front. (Biobank-C20)

TABLE 8

"what if researchers find a change in a gene that might be related to the disease they are studying, but they are not sure if it is or what it means?"

Response	Theme	Examples
Should offer	Explain purpose of recontact	• Yes, I think, people would want to know. You know, "Why are you being a vampire and taking my blood again?" (laughs) I just don't want to give away blood willy nilly. (Epilepsy-D04)
	Information is valuable	• Well, again it's—I think yeah. The participant would want to know everything that they could get their hands on. (Biobank-C15) • It's all still good information. (Autism, SAGE-S22)
	Right to know	• As long as the researcher is clear and tells them they are not sure what it means, I think people should have the right to know that. (Autism, AGRE-S18)
	Personal responsibility	• Because if I have an abnormality in a gene, I'm going to remember that, I'm going to write it down. And then as I do my end research, I can see where someone else is working on that gene or whatever, will catch my attention. No one is going to monitor it any better than I am. (Autism, AGRE-S10)
Should not offer	Undue worry, distress	• I think that would do more harm than good… If you can't be 100% sure, then don't tell them because that's just gonna give them worry. That's just gonna make them think "Oh my God. Am I—what's gonna happen to me? What's gonna happen to my kids?" (Biobank-C12) • No. No. That's a perfect example of when not to, because you don't know. And you give somebody some information, they're just going to go with it and assume the worst. (Epilepsy-D16)
	Not "information"	• Those are not real knowledge. It's not truth yet. It's a speculation. It's a hypothesis. It's a guess. And I don't think that's fair to put that in somebody's head. (Biobank-C09)
	Misunderstanding, confusion	• It puts more of a question mark in the person's head as whether or not they're all right or something's going to get worse. And it makes them more confused. (Epilepsy-D03) • If it's unclear to a researcher what it might mean, then I'm not sure if I can make any head or tail of it either, so I may not necessarily need to know that. (Autism, AGRE-S13)
Uncertain	Unsure	• That one can be kind of a mixed bag. It can kind of go between people that might take the information just for the sake of having all the information necessary in case it becomes relevant, but then there's some people that might … nitpick and be overly worried that they have this gene and freak out about it. (CF-C17)
Other	It depends	• I think you have to look at the whole situation. How bad is their situation? How far gone is their disease? You have to weigh everything in … and then the individual themselves. That could be tough to answer. That could really be tough. (Epilepsy-D14)
	Inform physician	• The patient's doctor should know. The patient should let the researchers know who their doctor is. And maybe the doctor should tell the patients, if the doctors know what to do. But let the doctors make that call. (Epilepsy-D28)

TABLE 9

"what if researchers find a change in a gene that they are pretty sure is related to the disease they are studying, but there is no treatment or anything different the person could do based on that information?"

Response	Theme	Examples
Should offer	Information is valuable	• I would still want to know. There may be a cure for epilepsy, there may not. There may be a treatment, there may not. But I want to know everything I can about epilepsy, good, bad and ugly. I just want to know everything 'bout it. (Epilepsy-D29)
	Answers	• Yeah it would be good to have that information simply because it helps you understand why you're experiencing what you're experiencing. Whether there is a treatment or not. Certainly answer a lot of the questions. (Epilepsy-D07)
	Future interventions	• You might as well know because there might be a treatment, and then if you hear on the news, "Oh, you know this study done two years ago found this. Well, the researchers have recently identified a drug that's able to handle that." Somebody's going to call up their doctor. (Biobank-C18) • Even if you can't get a treatment now there is always a hope for treatment down in the future. (Autism, AGRE-S09)
	Immediate benefit, personal utility	• Even if there wasn't a treatment maybe there's some things you could do to lessen the severity or, you know, if you exercised more or something like that, that it somehow would at least help the situation. (Autism, SAGE-S21) • Let's say they found the chromosome that caused autism, but even if there was nothing that they could do prenatally to fix it, it might be nice to know "Hey, here's your percentages of having another kid with autism." I still think it would be good for people to know to make informed decisions. (Autism, AGRE-S02) • Let's say you discover a gene that's going to make me die in five years. If you tell me that I have this gene, I can plan my life, you know, I can do my estate planning or whatever. I would live my life differently knowing that I was going to die sooner. (Autism, SAGE-S25)
Should not offer	Undue worry, distress	• That's something they really don't need to know if there is no cure for it. It would worry somebody. (Epilepsy-D24)
	Misunderstanding, confusion	• I mean if there's no way to treat it … the average person is not gonna be able to understand "Oh. Something's wrong with this gene." I mean they are not going to know what that really means. (CF-C03)
	Continuing uncertainty	• If there's nothing you can do about it, and it's not a—it'd be one thing if that gene is 100% correlated to a condition… [but] there are a lot of genes that are correlated to a lot of things that just never happen in a lot of people. (Biobank-C10)
Uncertain/Other	It depends	• Well it kind of depends on the situation the person is in. If they have high hope (laughs) they probably shouldn't know at all. Or it's just hard to answer. (Epilepsy-D01)

TABLE 10

"How important would it be to you to find out what researchers learned about the role of genes in [original condition] in general, even if you did not get your individual genetic research results?"

Response	Theme	Examples
Important	Outcome of contribution	• I would like that. That would be very interesting. It would be nice, if I participate in a study and a paper is written, to get the paper even though I wouldn't understand probably the abstract, but I could look through it and see that I feel that I've made a contribution. Whether mine actually helped or not I can at least think it did. (Biobank-C10) • It's important to know what they're doing, why they're doing it. They're not just coming around and giving you a test and saying, "Okay, filled out, see you later." No, you'd like to know that your time and effort is getting some kind of results. (Epilepsy-D06) • I mean I'm curious, "Has this helped anybody? Have they found any great answers? Are they coming up with new methods?" (Diabetes-S08)
	Stay updated	• It's important to me. I find the research interesting and obviously we have a personal interest in it, but even if the information wasn't something that was going to be directly applicable to my family or something, I think it's helpful to know. I want to know as much as I can. (Autism, SAGE-S24)
	Provide information to family	• Even if I don't know for a fact it's for me, it would allow me to know that a possibility is there that it could be hereditary. And that it could still be something I could look for in my kids. (Epilepsy-D29)
	Answers	• It would be very important. I mean I think it would make me understand exactly how my daughter got it. (Diabetes-S03)