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Incidental Findings of Therapeutic Misconception in Biobank-Based Research

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Abstract

Purpose—This paper explores expressions of therapeutic misconception in a deliberative-engagement project focused on the return of aggregate and individual genetic results from biobank-based research.

Methods—We enrolled 45 self-described African Americans in a deliberative-engagement project to explore their attitudes regarding the return of results from biobank-based research. Four groups of individuals participated in four sessions over two days that included both educational and focus-group components.

Results—Therapeutic misconception was expressed by individuals from both clinics on each day that they met. Three main typological categories of therapeutic misconception were noted: 1) the reasons for consenting to participate in a biobank; 2) the conflation of research with clinical care; and 3) mistrust about the meaning of biomedical research findings.

Discussion—While trust may explain why some research participants express therapeutic misconception, it was also fueled by mistrust (for example, a disbelief that a condition described as untreatable was truly untreatable). We also found that therapeutic misconception is not due solely to research participants' misunderstandings, but is a bidirectional phenomenon that can be exacerbated by researchers. This finding raises questions about how to engage prospective research participants in the long-term goals of biobank-based research without unintentionally overstating possible short-term clinical benefits.

Keywords

therapeutic misconception; trust; biobank; return of results; deliberative engagement

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Introduction

In 1982 Paul Appelbaum and colleagues described therapeutic misconception (TM) as the failure of prospective research subjects to grasp the difference between medical research and clinical care.[1] The authors noted that this phenomenon occurs “especially, but not exclusively, in therapeutic research.”[1] Over the next two decades, a number of studies confirmed the ubiquity of this finding in clinical trials,[2-7] and there are some data to show that it occurs in biobank projects.[8,9] In 2009, Ormond and colleagues described it in participants of a population-based biobank.[8] This finding was replicated most recently by Lakes et al., who performed focus groups in a variety of communities of different ethnic and cultural backgrounds about possible enrollment into the National Children's Study, a United States pediatric population-based biobank.[9] While they found that participants in all groups expressed the belief that there would be both societal and personal benefits, the researchers observed that Spanish-speaking participants expected benefits in a way akin to the expectation of benefit from participating in a social-service program.[9] The findings by Ormond et al. and Lakes et al. are troubling because if prospective participants do not understand the purpose of the research in which they are being invited to enroll, their agreement is not an informed consent, which is required of ethical research.[10-11] This is further complicated for enrollment in biobanks, for which researchers seek broad consent to use the samples and data for purposes not yet identified and by methods that may not yet even be developed. While misunderstanding the nontherapeutic purpose of the research may yield higher participation,[3] it may also backfire if participants become angry at and resentful of the researchers and the research itself upon realizing that they will not receive immediate clinical benefits.[4]

We conducted a deliberative engagement with African Americans on the South Side of Chicago in order to explore attitudes about biobanks and the return of individual and aggregate research results. A deliberative engagement involves educational programs followed by focus groups in order to identify the attitudes and values of an informed public. It differs from a deliberative democracy, which seeks population representation and specific policy recommendations.[12-14] In this manuscript we describe the incidental finding of TM in our deliberative engagement project. Specifically, we examine two issues not addressed in the literature: 1) what factors play a role in generating TM in biobank-based research, and 2) the way in which short educational sessions combined with peer discussions affect TM.

Materials and Methods

We recruited individuals from two clinics on Chicago's South Side – from a Federally Qualified Health Center (FQHC) that provides care mainly to publicly insured families, and from a university-based practice (UBP) that provides care mainly to privately insured families. Our recruitment advertisement (available from corresponding author on request) specifically stated that we were not performing diagnostic testing, but rather were collecting the community's opinions about biobanks. During the consent process our participants were informed that “[t]here are no clinical benefits” from participating in our study but that “the information [they] provide us may improve the policies of biobanks in Chicago and nationally.”

A complete methodology is provided elsewhere.[15] Participants attended four two-hour, deliberative-engagement sessions over a period of one week (two sessions on two consecutive Saturdays). Each two-hour session consisted of an educational presentation followed by focus-group discussions with structured questions and prompts. The first day consisted of two sessions in which the educational component focused on 1) basic concepts, including the difference between research and clinical care, genetics, biobanks, and genetic research; and 2) biobank structure, function and governance. Both risks and benefits of genetic research and biobanks were detailed. While we mentioned the various types of biobanks (disease-based, cohort-based and population-based), we explained that we would be concerned with the creation of a population-based biobank at the University of Chicago that would seek to enroll all patients who receive care as both in- and outpatients. We explained that this type of biobank would collect data through routine clinical practices, and would not require participants to provide other health information or samples. We specified the difference between clinical care and nontherapeutic research on its own slide.

The educational component of the two sessions on the second day focused on 1) the return of aggregate and individual genetic results to donors and 2) the return of child donors' results. Six types of results that might be generated by biobank-based research were discussed: 1) results about treatable conditions; 2) results about untreatable conditions; 3) information about reproductive risks; 4) incidental results (e.g., misattributed parentage); 5) results with uncertain meaning; and 6) results that would not have clinical impact but might have personal meaning (e.g., predisposition to thrill-seeking). We explained that some biobanks were designed never to return results and that others were open to returning results but were seeking guidance about 1) whether to return only aggregate results or both aggregate and individual results, 2) what criteria should be met to permit the return of results, and 3) how to return research results efficiently.

In the focus groups on the first day, participants were asked to comment on their attitudes regarding the pros and cons of participating in research and, more specifically, regarding enrolling in a biobank. They were also asked to discuss their attitudes regarding giving broad consent to future research using the collected samples versus being recontacted to consent to specific types of research using the sample. In the focus groups on the second day, the participants were asked to comment on their interest in having aggregate and individual results returned. Three types of conditions were discussed: 1) gene changes resulting in an untreatable condition like Alzheimer disease; 2) gene changes that have no known health effects and whose meaning researchers have not yet elucidated; and 3) gene changes that are more common in people of a specific racial or ethnic group. All data in this paper come from these focus-group sessions. The full study methodology is provided elsewhere.[20]

Focus-group discussions were transcribed from tape-recordings of our sessions and independently reviewed by two investigators, who also compared the dictation to notes taken during the sessions in order to ensure accurate dictation. Transcripts were uploaded to Atlas.ti (version 6), and two investigators working on the overall research project coded the transcripts in Atlas.ti (version 6) using a codebook developed through an iterative process and after reaching standard intercoder reliability. The codebook specified inclusion and

exclusion criteria in order to assist in the identification of key opinions and themes. Participants are identified by site of recruitment (Q=FQHC, U=UBP), by gender (F=female and M=male), and by a unique number based on our coding method.

As is common practice in qualitative analysis, themes that emerged from the data, but were not anticipated in advance, were added to the codebook. This was true for TM, which was added initially after several examples of the conflation of clinical care and research emerged. Although our code for TM was defined as the conflation of clinical care and research, during analysis we found examples of TM in comments that were coded as consent and trust, and these were incorporated into our coding schema as well. In this manuscript, we report on the incidental finding of TM and describe the three main typological categories of TM that we found during our deliberative engagements.

The study was approved by the University of Chicago's and Northwestern University's Institutional Review Boards, which waived the requirement for written informed consent because the interventions posed minimal risks and were interventions that would not require written consent outside of the biomedical research arena.

Results

Deliberative engagements were conducted with 4 four groups consisting of 45 adults who self-identified as African American. The first two deliberative groups enrolled 22 participants whose children received care at an FQHC, where over 90% of the patients self-identify as African American. The other two deliberative groups enrolled 23 participants whose children receive care at a UBP, which provides care mainly to those with private insurance and where approximately three-quarters of the patients self-identify as African American. Approximately three quarters of deliberants from both healthcare facilities were female, and the average age was 40 (range: 20-63). Overall, 22% had a high school diploma or less, 58% had some college, and 20% had a four-year college degree or more, with greater educational achievement in participants from the clinic providing care to those with private insurance (see Lemke et al.[15]). Only two participants (one from each healthcare facility) did not complete all four sessions.

The code for TM was uncommonly used, but occurred more frequently in the FQHC focus-groups than in the UBP focus-groups. Overall, TM was expressed by over half of the individuals in the FQHC and less than 20% of individuals in the UBP. Expressions of TM were found twice as frequently on the second day compared to the first day. We describe three typological categories of TM: 1) TM as an explanation for providing broad consent, 2) TM as the conflation of clinical care and research, and 3) TM expressed as skepticism about the meaning of biomedical research findings.

Category 1: Therapeutic misconception and the informed consent process

TM was expressed mainly on the first day in discussions about the reasons to consent to participate in a biobank. While participants were informed in the preceding educational session that broad consent means that an individual provides permission for samples to be used in multiple disparate studies, several participants stated that giving broad consent

would allow them to receive the largest range and amount of results: “I need to … have some research done on me: How did I form kidney stones? I would be broad; just test me for everything” (QF02). “If someone can give their broad consent, I think by that same token they should be able to receive all the information back in a broad way also” (QM04).

Similarly, while participants were told that an alternative to broad consent was to be recontacted and reconsented for each research project, some individuals stated that they would want to be recontacted and reconsented in order to ensure the return of results. As one participant explained, “Come back and contact me, because – like I said – if I got schizophrenia or bipolar, I want you to come and tell me” (UF07). This participant erroneously believed that if researchers could not move on to a new project without first getting the participants' reconsent, it would guarantee the return of results from the previous study.

Category 2: Conflation of research and clinical care

The traditional conception of TM, the conflation of research and clinical care occurred mainly on the second day. We found that some participants believed – despite explanation to the contrary during both the educational and focus-group session – that through biobank participation they could receive clinical care. One participant said she would not enroll her child in a biobank unless “something [was] extremely wrong” (QF01) with him, and then she would use the biobank to conduct research on him in order to find out what the issue was. Another woman stated that she was “totally for biobanks” because they “give an opportunity to those who don't have any insurance … ‘cause a lot of times you can't get all the necessary tests [without insurance]” (UF09). Finally, one woman suggested that primary-school teachers should be involved in biobank governance as they “spend a lot of time with our children” (UF16) and could tell researchers what symptoms the children might be presenting – and even how they were reacting to medication prescribed as a result of their participation in the biobank.

When explicit confusion between medical research and clinical care arose, discussion facilitators generally reminded participants that the topic at hand did not involve studies in which they might receive direct healthcare benefit. On several occasions participants corrected other members of the focus-group session: “This is not [about] a clinical study, where it might be toward the individual,” one woman reminded the group, “*because it's research*” (UF10). In several sessions, a chorus of participants would remind peers who raised clinical-care issues of the facilitator's caution, “Remember, this is research.”

Category 3: Therapeutic misconception and mistrust

The third category of TM was participants' expression of skepticism about the meaning of biomedical research findings, which also arose mainly on the second day, In discussions of the return of results, we found expressions of TM based in mistrust that: 1) the untreatable is truly untreatable and 2) the unknown is truly unknown.

The first category of mistrust causing TM involved discussions of whether untreatable conditions were truly untreatable. When participants were given a probe that asked whether

they would want to receive research results about an untreatable genetic condition, several participants responded that they would want them in order to seek out treatment. One participant said, “I would try to find out if I could get treated” (UF05), and another responded that there exist “certain drugs that can curtail [the untreatable condition] so it won't be as bad as it is” (UF15). A third said she would use information about such a condition in order to “take preventative measures” (QF09).

Some participants also expressed mistrust that genetic changes of unknown significance were truly unknown by professionals. Participants were told that if they were to ask the researchers what such gene changes meant, the researchers would respond, ‘We don't know.’ If they were to ask other geneticists, the same answer would be given. Nevertheless, several participants expressed doubt that the meaning could actually be unknown. One stated, “I am going to someone else who possibly can tell me what it is” (QF05). Another individual said that one's primary caregiver should be informed of biobank-based research results, because he or she “might want to do some tests to see, or the doctor might have some knowledge about a different gene and stuff maybe that can help you out, or give you to somebody who can see what the gene means or something” (QF10). A male participant stated that his personal physician would not need to see the results from his participation in the biobank because the physician “already know[s] what's going on, because [s/he] do[es] full check-ups and physicals and stuff like that” (QM05).

Some participants struggled to understand that genetic research is conducted both to identify novel genetic changes and to determine whether they have clinical significance. The participants struggled to understand that the goal of research was to discover new knowledge that would advance science. Rather, several participants suggested that they would determine its meaning through personal investigation. One woman said she would “try to put it all together” in order to discern “where all this stuff [disease] came from” (QF08). A second participant stated that if the researchers were to tell him they did not know the implications of a certain gene change in his child, he would instruct his child to “go grab a dictionary and look it up” (QM05). A third qualified her ability to self-interpret by explaining that first she would need to “be taught – just like we sitting in here [at the deliberative-engagement session], learning about stuff. We should be taught to test our own stuff” (QF05). This participant wanted to attend educational sessions where she would learn how to “test [her] blood” and find out that “I've got this, this, and this. I don't got that, but this, this and that” (QF05).

Discussion

When Appelbaum and colleagues described TM in therapeutic research in 1982, they hypothesized that it could occur in nontherapeutic research.[1] Like Ormond et al.[8] and Lakes et al.,[9] we confirm this hypothesis. While TM comments were not overly common, they were nonetheless expressed by individuals from both clinics and on each day that they met. Interestingly, the type of TM differed between the two days with greater focus on TM in consent on the first day and greater focus on TM resulting from the conflation of clinical care and research and from distrust on the second day.

Previous studies have found that TM occurs because research participants place excessive trust in their physicians and fail to understand how the physicians' role changes in the clinical research setting.[16] The extent of this conflation should not be underappreciated given that at least one participant expressed a belief that biobank participation could make up for lack of insurance.

Lidz and Appelbaum have questioned whether African Americans may be less at risk of TM due to greater suspicion of research and researchers.[4] We found, however, that TM can occur as a results not only of trust but also of mistrust. Some participants were skeptical of our statements regarding ‘untreatable diseases’ and ‘results with unknown implications.’ They thought that certainly *someone* would know what the results meant or how to treat a so-called untreatable condition identified by biobank-based research. Such comments presupposed that all the knowledge and therapies needed for quick analysis, treatment, or cure already existed.

Appelbaum also noted that TM is not due solely to research participants' misunderstandings but is a bidirectional phenomenon that may be fueled by the researchers.[5] Appelbaum states that one of the causes of TM is “the confusion that exists in the minds of the researchers themselves regarding the differences between rendering treatment in clinical and research settings.”[5] Appelbaum does not believe this to be due to ill-intentioned researchers; he does, however, argue that the first step to disabuse research subjects of unrealistic beliefs will be to change the way in which investigators approach prospective research subjects. Others have pointed out that TM may be exacerbated by “frame effects.”[17] Framing occurs because much research takes place in clinical settings in which participants are used to getting medical care.[18-19] Similarly, physicians acting as researchers may send mixed signals to participants – doctors' white coats and previous relationships with individuals *qua* patients may lead participants to believe they are getting clinical treatment.[3] Furthermore, when patients participate as research subjects regarding their own health concerns, they may not escape the “psychology of illness,” which leads them to hold out hope that they will benefit from research, despite assertions to the contrary.[3]

We tried to distinguish clinical care from biobank-based research during enrollment for our deliberative engagement. We recruited participants from pediatric waiting rooms in which they were not patients but were accompanying their child(ren). The recruitment material, verbal-consent script and educational slides specifically stated the nontherapeutic nature of our project. When participants made comments that suggested confusion between clinical care and research, facilitators generally reminded participants that they were not being asked to discuss studies in which they might receive direct healthcare benefit. Fellow participants often echoed this reminder as well.

Despite our attempts to distinguish biobank-based research from clinical care, the focus of the second day was on the return of research results. The suggestion that results of biobank-based research could have clinical relevance or incidental or personal meaning might inadvertently have fed into TM.[20] Thus, discussions about returning results with the public represents a serious tension in the design of biobanks, a tension that was not resolved by our educational instruction or the proceeding peer discussions on the issues. Our participants

believed that medical research, like clinical tests, was used to describe a participant's genome in terms of previously established facts correlating genotype with the expression of disease and disorder. Because of this they believed that they could receive medical care for things discussion facilitators described as unknown by the medical research community. The researchers – instead of torchbearers for new science – were seen as clinical laboratory technicians, providing the groundwork for currently possible medical care.

Unfortunately, we are unable to definitively conclude that our educational sessions and peer discussion exacerbated or ameliorated TM. While we are able to document different types of TM expressed between the two days, this may be due to the content and structure of the daily programs. Since we had not anticipated uncovering TM, we only had one slide on the first day that specifically discussed the difference between research and clinical care, a concept that may have been worth repeating on the second day. However, given the more common codes for TM on the second day, it seems reasonable to conclude that the educational sessions and focus-group discussions about the potential benefits and harms of returning research results were interpreted to mean that findings of interest to participants would be discovered routinely. A decision not to report these results was understood as withholding clinically relevant information and not due to the lack of clinical validity or utility of the information.

Our interpretation that our research project may have exacerbated the conflation of research and clinical care challenges the current arguments that support returning results based on participant interest.[21-25] The mere offering of the return of results may suggest greater clinical utility and validity than is warranted and may exacerbate confusion between the goals of clinical care and research. Additional research is needed to determine whether alternative educational approaches can minimize TM and its potential impact on public consensus about how, why and when to return research results to biobank participants.

A limitation of our findings regarding the causes of TM in population biobank research is that we were not actually enrolling participants into an actual biobank but only seeking their guidance in designing a population biobank. To the extent that those who mistrust the research enterprise are less likely to enroll in an actual biobank, TM caused by mistrust may not be a problem in over-recruitment. It may, however, cause problems in retention if participants decide to withdraw when no results are returned in the short timeframe in which they expect them.[4] Given the importance of enrolling and retaining large, diverse populations in biobanks, steps must be taken to reduce TM in order to ensure participants' understanding about the goals of the research to which they are consenting.

A second limitation of our findings is the generalizability of our findings. We intentionally recruited African Americans from the South Side of Chicago for the larger project because their voices have been underrepresented in the biobank debates to date. To our credit, we did recruit participants who had diverse educational achievement from two healthcare facilities that serve very different socioeconomic communities, and we found TM expressed by many. Since all participants were African American, though, we cannot prove that our findings of expressions of TM in biobank-based research are generalizable to other ethnic or geographic communities. However, other studies that have commented on TM suggest that it is rather

ubiquitous. Lakes et al. found the conflation of research and service particularly strong in the Hispanic community[9] and Ormond et al. found it in a mainly college-educated, Caucasian population.[8]

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