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Harms of Deception in FMR1 Premutation Genotype-Driven Recruitment

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The research study in question proposes to recruit female participants with the FMR1 premutation from a biobank and evaluate their clinical symptoms and phenotypes, without disclosing the purpose of the study or participants' personal FMR1 status at any point during or after the study. The case asks two ethical questions about the nature of the study: whether the design as currently proposed is (1) harmful or (2) deceptive. We identify three ways that the research proposal is harmful, and we ultimately conclude that because of these harms, deception is not justified, and the research cannot be conducted ethically in the absence of disclosure.

The first harm of nondisclosure relates to knowledge of personally relevant health information. As currently proposed, women in this study who have medical conditions caused by the FMR1 premutation would not receive important information about their own health status. While concerns about the premutation are commonly focused on the potential for transmission of an expanded copy to offspring, 20% of women with the premutation have primary ovarian insufficiency (POI), which manifests as diminished fertility or infertility (Hantash et al. 2011). There is evidence that women who have experienced fertility problems such as POI wish to receive their personal FMR1 premutation status if offered testing and view premutation status as potentially explanatory as to the underlying cause of their fertility challenges (Pastore et al. 2014). This suggests that a portion of women in the study cohort have strong interests in understanding their own health conditions to mitigate anxieties and for purposes of clinical planning, and would be deprived of this if the researchers choose not to disclose.

The second harm of nondisclosure relates to missed opportunities for reproductive planning. We believe that many asymptomatic women in the study cohort would want to know their premutation status. While no surveys have been done on this precise question, there is clear evidence that asymptomatic women wish to know their full mutation status for two reasons: the possibility of termination, and planning for future fertility issues associated with FMR1

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(Anido et al. 2005, Archibald et al. 2012). Both of these reasons are relevant to carriers of the premutation. There is a chance of having offspring with Fragile X, because the premutation can expand during reproduction. Women with the premutation also have fertility challenges. It is therefore likely that asymptomatic women in the study cohort have reproductive interests in their premutation status, and not disclosing this valuable information would hinder or limit the reproductive choices these women have.

These first two harms relate to a failure to divulge useful information. However, even if participants have an interest in receiving this information, do researchers have a corresponding obligation to disclose? Answers to this question often focus on broad ethical duties to disclose results, such as a duty to rescue, but here we focus on three contextual factors that help determine when disclosure is warranted: benefit to participants, uniqueness of researcher access, and burden of disclosure (Gliwa and Berkman 2013). All three factors support an obligation to disclose genetic information in this particular study context. First, disclosing the premutation is likely to benefit participants by helping women with POI understand their condition and providing an opportunity for reproductive planning for all women in the study cohort. Second, the researchers likely have unique access to participant's carrier status, since the FMR1 premutation is not usually screened for during genetic testing. Finally, disclosure carries a low burden for the research team, since each participant's genetic status is already known. The researchers are therefore in a unique position to improve the welfare of participants at low cost to the research effort, indicating an obligation to disclose.

There are also potential concerns about harms of returning genetic information to participants. One concern is that unanticipated disclosure could provoke anxiety. However, this is unlikely to outweigh participants' strong interests in knowing the information, since women who learn they are FMR1 carriers go through an adaptive process involving coping behaviors that lessen their level of upset (McConkie-Rosell et al. 2001). In addition, the study cohort, at 56 years old on average, is past typical childbearing age. Nevertheless, women show an interest in "the effects of their [FMR1] carrier status on their children and grandchildren" (Anido et al. 2005). This suggests that carrier status is welcomed even if it does not affect personal reproductive decisions, consonant with a broader conception of reproductive autonomy.

The third harm of the study results from unexplained referral to medical care. The researchers face a dilemma because the participants understood that they would not receive results, yet it seems apparent from the case description that the team expects to find clinically relevant information and considers it important to fulfill their ancillary care duties to maximize indirect benefits to participants. However, it will be difficult for the participants to be directed to medical care without revealing health-relevant genetic information. Referring participants to medical services without telling them the underlying reasons why is likely to provoke confusion and anxiety, especially in those who have experienced clinical symptoms. Even if there were clear scientific necessity not to disclose mutation status to participants at the outset of the study, for example, due to a risk of biased symptom reporting (which is not an argument that has been presented by the researchers here), the information

is not time sensitive and participants could be debriefed after their participation in the study is complete.

In order to evaluate these harms in context, we must note our view that this research is deceptive, given that the informed consent process withholds key information about the study such as its purpose and why participants were contacted to participate. The fact that research is deceptive does not necessarily mean it is unethical. Deception research can be justified when, for example, it is essential to answering an important scientific question. Such research has to comply with federal regulations that limit the kinds of deception research that can be conducted. Acceptable research must be of minimal risk, cannot be practicably carried out without a waiver of informed consent, the waiver must not affect participants' rights and welfare, and participants should be debriefed after if appropriate (45 CFR §46.116.d: Department of Health and Human Services 2005). We believe that the study fails at least one of the required tests for research involving deception by neither disclosing health-relevant information, nor even giving participants a choice about whether or not to receive this information. This omission negatively affects participants' welfare by depriving them of information they value for their personal health and reproductive interests—information that may be relevant to their choice about whether to participate in the research. Given the harms identified in this commentary, we do not believe the research can be conducted ethically in the absence of disclosure and informed consent. Details of the consent process are beyond the scope of this commentary, but researchers could consider a sequential consent process (e.g., Beskow et al. 2012) that entails sending a nonspecific letter to all potential participants, both controls and those with the premutation, explaining the topic and purpose of the study and providing an opt-in to the study and to receiving personal results. Alternatively, a modified process involving debriefing before referring participants to health care services could help to mitigate concerns about harms of nondisclosure.

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