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When there are only two who can tango: ethical concerns at the juncture of highly novel interventions and precisely targeted research populations

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_____ Among the many instructive features of the case study about the preventive trial for autosomal dominant Alzheimer's [disease](#) is how it illustrates the impact of new technologies on research. Advances in fields such as genomics, genetics, and stem cell research are leading to the development of precisely targeted and often truly novel interventions that, if successful, will represent true game changers in the treatment of serious diseases such as Alzheimer's [disease](#). But there is much to learn along the arduous path to enhanced benefit, with critical ethical issues at each juncture. As this study illustrates, one of these junctures arises from the fact that, because the intervention is so precisely targeted, it requires recruitment from a small subset of the population affected by a disease. In this brief commentary, I focus on two co-mingled ethical issues that can accompany such targeted recruitment. One is the relatively high "price of admission" that can be required for entry into a trial and the other is the extent to which consent for participation may be a "foregone conclusion" for many of these individuals.

_____ As experimental interventions become more targeted, the research community becomes increasingly dependent on access to narrowly defined populations, populations that in turn must disproportionately bear the demands imposed by early

research protocols studying novel developments. How high can we reasonably set the price of admission for these prospective research participants-subjects in order to facilitate the precisely targeted research? The price of admission may go far beyond being subjected to the risks of a new intervention. Invasive monitoring procedures, such as a lumbar puncture, or surgical procedures may also be part of the protocol. (A For example, a recent Phase I study of a stem cell intervention to study ALS required participants-subjects to undergo a laminectomy (Riley et al., 2014).¹)

_____ These burdens of participation can push the limits of what we normally are inclined to tolerate for early trials, but the new technologies can require imposing such risks at the very outset in order to be able to test new approaches. This is especially challenging given that the likelihood of personal medical benefit for trial participants-subjects is remote. For example, there is no escaping the high failure rate of vaccine and other pharmaceutical trials. Indeed, 85 to-90 percent% of all investigational trials fail to lead to FDA-approved interventions (Davis, 2011 and DiMasi 2003).^{2,3} We always hope that novel developments, such as being able to so precisely target a treatment, will increase the odds of success—but that hope, we must recognize, is speculative, while the burdens imposed by the protocols are genuine and possibly quite serious.

_____ With respect to this vaccine trial, we must consider the consequences of requiring a predictive genetic test so that researchers can be assured that they can study the targeted population. While participantssubjects can request shielding themselves from the results of the predictive test, the fact of the matter is that a price of admission to the trial is the discovery of predictive knowledge that the participansubject might desire under different circumstances never be known, by anyone. Thus, someone

from the affected community who wants to see the research go forward must submit to what is otherwise an undesired procedure. This could lead to a range of undesirable consequences.

_____ Due to their involvement in the vaccine trial, ~~participants~~ subjects may focus more than they otherwise would on their risk for Alzheimer's and they may have a tendency as a result to over-attribute a range of health symptoms to Alzheimer's, likely increasing their -pondering about whether to undergo predictive testing. Knowing that there is someone who already knows their test results might create additional pressure for people to learn what they otherwise would prefer not to know. In other words, a preferred state of ignorance may be easier to maintain when specific test results are merely a possibility rather than a reality. In this instance, it becomes a matter of you learning what someone else already knows about you. What was once a mystery to all and in the hands of fate is now simplyjust hidden from you; ~~and~~ this may push people to obtain predictive information that they would never otherwise pursue if not for their trial participation.

_____ To fully consider the required forfeiture of ignorance imposed by this trial, we need to be mindful how novelty aggravates the concern. This feature of the trial may be of less concern, perhaps, in a different population. For example, we might be a little less concerned if the targeted research population were the Huntington's disease (HD) community, because that group now has decades of experience dealing with the availability of predictive testing. People affected by HD are now able to give prolonged consideration to whether, or under what circumstances, they would consider permitting a predictive test that may affect them. They can discuss whether or not this is

information worth knowing with a broad range of others, as well as observe others grapple with the same issues over time. The targeted population for the predictive vaccine trial lacks this important history and this fact may increase the psychological burdens posed by knowing that definitive predictive information is now known by someone and thus is fairly easily available to obtain for themselves. The only way to avoid this burden is to choose not to enroll in the trial.

_____ While non-participation is certainly an option, it may be a less likely and more difficult choice for some to make than we might suppose. This brings us to the co-mingled second ethical issue, the implications that targeting very specific, and thus likely small, groups of people can have for the informed consent process. Specifically, the more that a rare disease, or rare variant of one, is concentrated in families, there is a legacy of the disease. Longing for the time that the family is rid of the scourge of the disease or having a commitment to fight the disease in any and all ways available might easily be a part of the narrative arc in the lives of people in the affected community.

_____ Thus, consenting to trial participation may be an entirely characteristic decision for them to make, such that they will not be very motivated to learn much about matters such as risks and benefits. They may be more motivated instead to do what they can to contribute to a cure. This could in effect make trial participation a “foregone conclusion.” This should by no means disqualify them from participating, but the research community must take note of this feature of affected communities and explore what extra steps might be required in the consent process.

_____ These are just two concerns raised in settings like the preventive vaccine trial. Such trials highlight the extent to which researchers can be entirely dependent upon the

participation of small populations in order to carry out their research. At the same time, there likely will be substantial social and familial inertia for trial participation among the members of these populations, despite the risks and other burdens such participation may entail.

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