Ethics of genetic and biomarker test disclosures in neurodegenerative disease prevention trials

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ABSTRACT

Objective: Prevention trials for neurodegenerative diseases use genetic or other risk marker tests to select participants but there is concern that this could involve coercive disclosure of unwanted information. This has led some trials to use blinded enrollment (participants are tested but not told of their risk marker status). We examined the ethics of blinded vs transparent enrollment using well-established criteria for assessing the ethics of clinical research.

Methods: Normative analysis applying 4 key ethical criteria—favorable risk-benefit ratio, informed consent, fair subject selection, and scientific validity—to blinded vs transparent enrollment, using current evidence and state of Alzheimer disease (AD) and other prevention trials.

Results: Current evidence on the psychosocial impact of risk marker disclosure and considerations of scientific benefit do not support an obligation to use blinded enrollment in prevention trials. Nor does transparent enrollment coerce or involve undue influence of potential participants. Transparent enrollment does not unfairly exploit vulnerable participants or limit generalizability of scientific findings of prevention trials. However, if the preferences of a community of potential participants would affect the rigor or feasibility of a prevention trial using transparent enrollment, then investigators are required by considerations of scientific validity to use blinded enrollment.

Conclusions: Considerations of risks and benefits, informed consent, and fair subject selection do not require the use of blinded enrollment for AD prevention trials. Blinded enrollment in AD prevention trials may sometimes be necessary because of the need for scientific validity, not because it prevents coercion or undue influence. *Neurology*® 2015;84:1488–1494

GLOSSARY

AD = Alzheimer disease; **IRB** = institutional review board; **RCT** = randomized controlled trial.

Current guidelines recommend against testing for *APOE* mutations[1] or PET amyloid imaging for predicting Alzheimer disease (AD) in asymptomatic persons,[2] or support testing only within narrowly circumscribed conditions (e.g., for family or advance care planning) using nondirective counseling.[3] Although the use of such risk markers in asymptomatic persons is problematic in the clinical context, such testing has become pivotal in research. The cumulative biological effects over a long presymptomatic period suggest that intervening much earlier[4] in the process may be important to modifying the disease. This has led to presymptomatic treatment or secondary prevention studies targeting asymptomatic persons identifiable by various risk markers.[5–10] One ethical challenge of such studies is that they may test interventions with significant risks in persons who may never develop symptoms of dementia.

This article focuses on another ethical challenge of such trials; namely, the potential risks and burdens of disclosing risk marker results to participants. The knowledge that one will likely or certainly develop a devastating illness, for which there is currently no effective treatment, could cause psychological harm such as anxiety, depression, and stigma, disrupted family dynamics, and worries about loss of or failure to obtain insurance or other social and economic benefits

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such as employment.[11–17] Thus, many persons do not wish to know their risk marker status, even though they may wish to participate in a prevention trial.

Approaching such persons for a prevention randomized controlled trial (RCT) raises important ethical considerations. RCTs that would require disclosure of risk marker status as part of the protocol have been called coercive.[7,8] Designs that accommodate the at-risk persons' desire not to know[7,8,18] use blinded enrollment. In addition to randomly assigning risk marker–positive persons to experimental intervention or placebo, the trial enrolls a sample of risk marker–negative persons (who usually receive a placebo) so that enrollment does not equate to being risk marker–positive. In contrast, in traditional transparent enrollment, only those who are risk marker–positive are enrolled.

As advances in genomics and biomarker-based technologies lead to more prevention trials for neurodegenerative diseases, the question of which type of enrollment design—blinded vs transparent—is ethically optimal may become a frequently asked question. In the field of genetics research, people's right not to know their genetic information is widely (although not universally) defended, even when such information involves medically actionable data.[19,20] A similar argument could be made for biomarker results. Given these considerations, a systematic ethical analysis of enrollment design may be useful to investigators, institutional review boards (IRBs), and regulators as they design future prevention RCTs.

Prevention trials are of interest in several neurodegenerative diseases, including Huntington disease[7] and Parkinson disease.[21] Our ethical analysis of the optimal enrollment design for prevention RCTs primarily (although not exclusively) focuses on AD prevention clinical trials. AD is a devastating, lethal disease with a worldwide prevalence expected to reach 106 million by 2050.[22] AD RCTs are prominent and influential, and could potentially set a precedent for prevention RCTs in other fields. Further, AD prevention RCTs target enrollment using a variety of risk markers, ranging from dominantly inherited, highly penetrant mutations[8,18] to susceptibility mutations such as *APOE* ε4 and *TOM40* genes,[5,9] and biomarkers such as amyloid.[6,23] Some AD prevention RCTs are being conducted with blinded enrollment[8,9,18] while others are planning or are using transparent enrollment.[5,6] There is thus an opportunity to compare the ethical implications of various types of risk markers used in prevention RCTs.

The criteria for what makes clinical research ethical[24] are shared by major codes, declarations, and other documents relevant to research with human subjects: social value, scientific validity, favorable risk-benefit ratio, fair selection of subjects, independent review, informed consent, and respect for enrolled subjects.[24] For the purposes of this article, we assume that the research at issue has social value, will receive appropriate independent review (e.g., IRB review), and focus on enrollment rather than issues following enrollment (the focus of the respect for enrolled subjects criterion). We therefore focus on favorable risk-benefit ratio, informed consent, fair subject selection, and scientific validity. We argue that except for when scientific validity requires it, there is in general no ethical requirement for blinded enrollment. Notably, avoiding coercion is not the ethical basis for blinded enrollment.

Favorable risk-benefit ratio. Given our focus, we put aside the important ethical question of the intervention risks (i.e., potential for harm from the experimental intervention, especially when some participants are expected not to experience cognitive decline) and examine the risks and burdens of research flowing from blinded vs transparent enrollment.

Risks and burdens of transparent enrollment. People who volunteer for AD prevention trials with transparent enrollment will fall into 2 groups: those who are willing to know their risk status at baseline and those who desire not to know their risk marker status at baseline but whose desire to participate in a prevention trial exceeds that desire not to know.[25,26]

For those willing to find out their risk marker status at baseline, studies show that they will likely cope well with their results. These studies examined both early-onset AD predictive testing and *APOE* ε4 susceptibility testing.[27–31] The results are consistent with studies in Huntington disease and other neurodegenerative disorders.[32] A recent comprehensive review concluded that extreme, catastrophic reactions are rare, negative effects tend to be transient, people do not regret their decision (even among those who test

positive), and many report benefits of testing.[33] Informed persons who want to learn of their risk marker status therefore face little risk from that knowledge.[34] In fact, many want the opportunity to plan their lives with the information and find that knowledge reduces anxiety of uncertainty.[25,27,35] Although the number of persons in dominantly inherited mutation disclosure studies is small and long-term follow-up data are sparse,[36] disclosure of genetic information appears reasonably safe when the disclosure is desired.

In reality, however, an AD prevention RCT would also likely attract those who do not desire to find out their risk status but who would nevertheless accept testing and disclosure because they wish to be part of the prevention RCT. A small study of persons in families with dominantly inherited mutations for AD found that a significant minority of those (about 20%–46%) who would not otherwise want to know their risk marker status might be willing to find out their mutation status for the sake of participating in AD prevention trials.[25] How worried should we be about the impact of learning risk marker results on such persons?

Research on how people are influenced by and overcome the anticipation of negative medical news provides insights to this question. Patients typically overestimate both the intensity and duration of the impact of negative medical events.[37,38] This impact bias is largely due to the fact that people tend to focus exclusively on the negative event (sometimes called focalism) and fail to incorporate factors such as their ability to adapt and be resilient (immune neglect).[39] Importantly, this bias can be reduced by making people aware of their tendency toward focalism and immune neglect.[40] This suggests that when such persons are faced with a choice of entering a transparent enrollment prevention RCT, the choice may create an opportunity to see beyond the negative impact of a potential positive test result. For some, this may be enough to reduce their impact bias, leading to a decision to volunteer for the RCT.

Investigators using a transparent enrollment design can further reduce risks to subjects by assessing potential subjects' mood and well-being prior to testing and excluding those whose results suggest inordinate degrees of psychological distress.[31] These psychological and behavioral measures should be monitored over the course of the study.

Finally, transparent enrollment will allow researchers to study the effects of disclosure of risk marker status in a population broader than those who would desire disclosure at baseline, and will create data about people living with knowledge of being in an asymptomatic at-risk stage of a disease. The recent finding that older adults who learned their positive *APOE* status performed worse on measures of memory and self-rated measures of cognition[41] demonstrates the need to understand this phenomenon.

Risks and burdens of blinded enrollment. Research procedures are rarely flawless. Inadvertent disclosure of risk marker results could occur in a blinded enrollment design. Further, risk marker–negative persons, blinded to their result, may fear or infer that they are risk marker–positive from study participation (e.g., experiencing health problems not caused by the study but inferred as study side effects[25]). Some adverse events may require disclosure or de facto reveal the subject's mutation status.

Risk marker–negative persons enrolled in the blinded placebo cohort face considerable burdens, including regular study visits that demand time and include imaging scans, lumbar punctures, and, in some studies, placebo injections. These are not high-risk procedures but their cumulative burdens could be substantial.

Informed consent. ***Is transparent enrollment coercive?*** One major concern, expressed by investigators of blinded enrollment studies,[7,8] is that transparent enrollment is coercive, presumably because persons who are not willing to learn their risk marker status are pressured to accept disclosure in order to have the opportunity to participate in a prevention trial. If this rationale is correct, then informed consent in a transparent design may not be valid.

However, coercion is in fact not present. The Belmont Report defined coercion as occurring when "an overt threat of harm is intentionally presented by one person to another to obtain compliance."[42] Suppose an investigator offers a person participation in a transparent enrollment trial. A person who does not want to know his or her risk marker status may not be attracted to the offer, but the offer does not threaten the person with harm or threaten to take away a benefit he or she is otherwise entitled to. Not enrolling simply means the person does not have access to the potentially beneficial research intervention but that is not a violation of a right.

A related argument in support of blinded enrollment is that transparent enrollment presents undue influence. Undue influence is defined as "an offer of an excessive, unwarranted, inappropriate, or improper reward or other overture in order to obtain compliance."[42] But the investigator of a transparent enrollment trial is not exerting undue influence. An offer of participating in a clinical trial—which one can freely refuse—is not proposing an "excessive, unwarranted, inappropriate, or improper reward" and it is not offered as a means to force the person to learn his or her risk marker status.

In sum, even if blinded enrollment is sometimes necessary, it is not because transparent enrollment entails coercion or undue influence.

Special informed consent and disclosure considerations for transparent vs blinded enrollment. For transparent enrollment, there is a need to optimize people's understanding in several ways. First, some who perhaps reluctantly but freely agree to undergo testing may find out that they are risk marker–positive but then, after disclosure, find that they have a condition that makes them not eligible to enroll. This issue would be most pertinent for those prevention studies using susceptibility testing (i.e., *APOE* ε4, or amyloid) where it would be impractical to conduct extensive screening before the marker testing. For example, the A4 study performs a screening MRI after PET imaging disclosure, meaning some subjects who have elevated amyloid might be excluded based on their MRI results.[6]

Further, for transparent enrollment, the educational and counseling burden will be significant, given the current standards for genetic counseling for AD genetic tests and similar counseling needs for biomarker test results.[43] Disclosure of negative test results to those who are not enrolled will be challenging as well; explaining a negative genetic test result can be complex since being negative for a risk marker (e.g., not being a *APOE* ε4 homozygote) does not mean one is not at elevated risk for AD (e.g., due to age, or being a heterozygote).

For blinded enrollment, the potential subjects need to understand that even if they do not have a positive risk marker, they will be undergoing all of the procedures that marker-positive participants will undergo (except the active intervention), and that this will be only for research purposes to mitigate the need to disclose risk marker results. They should also understand that adverse events may lead to unblinding.

Fair subject selection. The criterion of fair subject selection requires that subjects (and communities) are selected for participation based on scientific objectives rather than on other factors and that the likelihood and distribution of the benefits and risks of research should be fair.[24]

Researchers should not design a study that exploits a vulnerable, conveniently accessible population—a practice that has been the source of spectacular ethics scandals.[44] But neither blinded nor transparent enrollment design raises this concern. Both people who are inclined to want to know their risk marker result and those who are not inclined are free to refuse participation. The other major fairness issue is that some populations face a lack of evidence-based diagnostic and treatment options because they have been excluded from research. This concern does not apply to either blinded or transparent designs. There is no scientific basis to argue that data from a transparent enrollment trial will not be generalizable to persons who prefer not to find out their risk marker status.

We are here considering fair subject selection criterion only in relation to the issue of transparent vs blinded enrollment. When a study is conducted in a relatively resource-poor setting, as in a developing country,[18] there may be special ethical considerations aside from the transparent vs blinded enrollment issue, but that is beyond the scope of this article.

Scientific validity. Considerations of risk-benefit ratio, informed consent, and fair subject selection do not yield an obligation to employ blinded enrollment for neurodegenerative disease prevention studies. The principle of scientific validity requires the use of rigorous methods to produce valid and reliable results[24] since an invalid study wastes resources and unnecessarily exposes subjects to risks. In some circumstances, scientific validity requires the use of blinded enrollment.

Highly penetrant dominant mutations that cause AD are rare. Thus, the number of persons available for prevention RCTs is relatively small. Persons who have a family history of autosomal dominant AD know they have as much as a 50% risk of carrying these mutations, and, if they do carry one, a near certain lifetime risk of developing a devastating illness. Although a recent study of persons at risk for early-onset AD found baseline interest in being tested (not actual tested rate) was 44% (15/34),[25] few people actually choose to be tested. A 2001 clinic-based study of persons at risk for dominantly inherited early-onset AD or frontotemporal dementia found that only 8.7% chose to be tested.[27] It is also reported that "almost no one" among persons at risk for familial AD in the DIAN registry chooses to be tested.[35]

Although most persons at risk for dominantly inherited mutation may not be willing to know their risk marker status, they may be motivated, having witnessed the impact of the illness, to participate in a prevention trial for self-regarding (hope for benefit), familial (desire to help one's own children), and altruistic reasons.[25] Further, those at risk for such mutations will likely be part of a community defined by that risk, whether at the family level or perhaps in larger clan cohorts or even a community of unrelated persons brought together by research registries or advocacy organizations.[35]

In such a situation, the scientific feasibility of the trials could be seriously compromised if one were to attempt a transparent enrollment design. If persons who at baseline wish not to know their mutation status choose not to participate, then a majority of persons at risk for the condition would be excluded. Further, the subset of persons who are not willing

to know their risk status but still desire to participate in a prevention RCT must choose between 2 unattractive options (not participate when they want to vs finding out their mutation status they would rather not find out). As discussed above, having to make such a choice does not constitute coercion or deny anyone his or her rights. But in such a setting, using a transparent enrollment design would be seen as insensitive to the preferences of the community of eligible persons.

This would have not only short-term consequences for the feasibility of recruiting from this pool of subjects but could also affect the long-term relationship between investigators and the community of at-risk persons. Without sufficient trust and collaboration of the community of eligible subjects, it would not be possible to conduct the research. Just as there is no right to participate in a research study (no subject can require that a researcher include him or her in a study), no researcher can compel anyone to participate in research. The only option is a mutually acceptable, voluntary agreement of cooperation. This highlights the importance of consulting the relevant communities during the early stages of trial design to determine their preferences. But the ethical principle that necessitates blinded enrollment in such a situation is, ultimately, scientific validity: a transparent design may not enroll sufficient numbers of subjects. The potential subjects' desire not to know their risk marker status does not create, of itself, an obligation to use blinded enrollment.

For other risk markers, the community standards around disclosure that create questionable feasibility may not apply. Trials that recruit using *APOE* ε4 and amyloid imaging differ in several ways from trials that target rare autosomal dominant mutations. The recruitment pool is much larger. There is high likelihood that people who are interested in knowing their risk marker status will self-select in volunteering for the trial; such persons will be more likely to see the test results as a potential benefit. Indeed, it may even be surprising to this group of persons if a blinded enrollment were proposed, because that design eliminates one of the benefits of participation. Also, since there is no socially identifiable group of persons defined by being amyloid-positive, for example, community considerations raised in the markers for early-onset AD will not be an issue.

There is one prevention trial using a risk algorithm that includes *APOE* and TOMM40 mutation results to predict AD in which the participants are blinded to their results.[9] That study has 2 official aims: a formal validation of the prediction algorithm in addition to a prevention RCT testing pioglitazone. The blinded enrollment is primarily necessary for rigorous validation of the prediction algorithm. Although some might argue that lack of validation of the algorithm ethically precludes disclosure of algorithm results to subjects, the situation is not unique. Amyloid imaging and *APOE* results for asymptomatic persons also have scientific support for use in research without explicit validation. Thus, the rationale for blinded enrollment in this study is to validate the prediction algorithm, not because the prevention RCT requires it.

DISCUSSION Our ability to identify persons at risk for serious neurodegenerative diseases will continue to run ahead of our ability to modify those conditions. In the clinic, testing for risk markers for such conditions is discouraged because there are no medical benefits to outweigh the psychosocial risks and burdens. However, the ability to identify reliable risk markers is crucial to conducting prevention trials. But many people, for the very reasons why the risk marker testing is discouraged in the clinic, do not want to find out their risk marker status. This is particularly true for persons from families with highly penetrant, dominantly inherited, devastating diseases such as Huntington disease or AD. Given that a similar combination of factors—an easily identified genetic marker for a serious condition that has no cure or treatment but that may be used to conduct prevention interventions—may occur for many diseases in the future, it is crucial to think about an ethical framework to guide design of such prevention studies.

Our analysis shows there are no special risk-benefit, informed consent, or fair subject selection issues that require blinded enrollment for such studies. Transparent enrollment is not coercive and does not present undue influence. However, investigators must in some situations use blinded enrollment in order to conduct a valid study. These situations are likely to occur only when the number of eligible subjects are limited and are part of an identifiable community whose values reflect a desire for blinded enrollment. The ethical basis for blinded enrollment in such a situation is the requirement of scientific validity, not the inherent value of the right not to know one's risk marker status. If it is feasible to conduct a scientifically valid study with transparent enrollment, then there is no ethical requirement to use blinded enrollment.

AUTHOR CONTRIBUTIONS

Scott Kim: study concept and design, drafting and revising the manuscript. Jason Karlawish: critical revision of the manuscript for important intellectual content. Benjamin Berkman: study concept and design, revising the manuscript for important intellectual content. All authors approved the final revised manuscript.

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