The ethics of disclosing genetic diagnosis for Alzheimer's disease: do we need a new paradigm?

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Introduction or background: Genetic testing for rare Mendelian disorders represents the dominant ethical paradigm in clinical and professional practice. Predictive testing for Huntington's disease is the model against which other kinds of genetic testing are evaluated, including testing for Alzheimer's disease.

Sources of data: This paper retraces the historical development of ethical reasoning in relation to predictive genetic testing and reviews a range of ethical, sociological and psychological literature from the 1970s to the present.

Areas of agreement: In the past, ethical reasoning has embodied a distinct style whereby normative principles are developed from a dominant disease exemplar.

Areas of controversy: This reductionist approach to formulating ethical frameworks breaks down in the case of disease susceptibility.

Growing points: Recent developments in the genetics of Alzheimer's disease present a significant case for reconsidering the ethics of disclosing risk for common complex diseases. Disclosing the results of susceptibility testing for Alzheimer's disease has different social, psychological and behavioural consequences. Furthermore, what genetic susceptibility means to individuals and their families is diffuse and often mitigated by other factors and concerns.

Areas timely for developing research: The ethics of disclosing a genetic diagnosis of susceptibility is contingent on whether professionals accept that probabilistic risk information is in fact 'diagnostic' and it will rely substantially on empirical evidence of how people actually perceive, recall and communicate complex risk information.

Keywords: Alzheimer's disease/genetic risk/genetic testing/susceptibility/genetic complexity/ethics/diagnosis

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Introduction

Most clinicians will be aware that disclosing genetic risk is a complex issue. Unlike other kinds of medical testing, genetic testing not only reveals the risk to an individual, but it also reveals the risk to other family members. Disclosure is ‘complex’ because the effects of genetic information may be wide ranging and unpredictable. In addition to the immediate or future consequences that information may have for an individual, a genetic test may reveal the risk to an offspring, it may have serious reproductive consequences for a family, the information may become a burden, it may lead to onerous obligations to disclose that risk to other relatives, and it may lead to stigma and discrimination. Research has shown that people can react to genetic information in very different ways, ranging from relief and resolution to denial and self-blame.\textsuperscript{1–6} Furthermore, people’s understandings of genetic risk can change over time.\textsuperscript{7}

Since the 1970s, ethical frameworks have been established to guide professional practice and to protect individuals and families from the potentially harmful effects of receiving a genetic diagnosis. The application of ethical principles grew out of professional concerns about the social–ethical implications of the ‘new genetics’. To a large extent, these policies were developed with a particular disease in mind, the extreme nature of which served as a model for other kinds of genetic testing. Predictive testing of Huntington’s disease (HD) became the benchmark against which other kinds of genetic tests were evaluated. However, new evidence has come to light that suggests that Mendelian disorders may not be a suitable model with respect to genetic testing for complex disorders. The ethics of disclosing risk for susceptibility to common complex disorders may require a new paradigm of ethical policy.

Such a paradigm may be justified if we consider the difference between predictive and susceptibility testing. What makes a genetic test ‘predictive’ is the identification of a dominant and highly penetrant gene that ‘causes’ a genetic condition. In other words, genetic testing is predictive of rare, Mendelian disorders. In contrast, susceptibility testing is a test for common disorders (they occur more frequently in the population) where there is no single causative gene action, but multiple genes (each conferring a small risk) interacting with environmental factors. If predictive testing is \textit{deterministic} then susceptibility testing is \textit{probabilistic} and thus highly contingent. The implication of the latter is that the inherent uncertainty of risk information significantly clouds its predictive and diagnostic potential.
The ethics of disclosing genetic risk: a brief history

The history of associating genetic diagnosis with ethics is a relatively short one. In the early 1970s, the availability of amniocentesis produced a stream of provocative articles that steadily acquired an ‘ethical’ character. In the *New England Journal of Medicine*, for instance, enthusiasm towards genetic screening programmes were greeted with cautionary reactions from ethicists and genetic counsellors who were keen to ensure that such programmes were guided by ethical principles. What concerned professionals was not so much the arrival of new screening technologies, but the complex moral and social domain that now appeared in relation to disclosing and calculating risk. Within the clinical setting, the complexity of decision-making and the greater need for ‘informed consent’ afforded new opportunities to establish principles of ‘non-directive’ genetic counselling. Prior to these events, there was no stable discourse on the ethics of disclosure or any sustained reflection on the communication of risk. However, from the 1970s onwards, a discourse on the ethics of disclosure grew out of an alliance between genetics professionals and medical ethicists.

Styles of ethical reasoning

Ethical reasoning on biomedical research and genetic diagnosis had acquired, by the 1980s, a distinct style. In the USA, we see evidence of this in the seminal President’s Commission for the Study of Ethical Problems in Medicine and Biomedical Research. Here, the Commission proposed several ‘principles’ to guide the design and operation of screening programmes, i.e. confidentiality, autonomy, knowledge, well-being and equity. Building on the influential Belmont Report and later developments by the Hastings Centre, ethical concepts provided clarity to professionals and protection to individuals regarding the potentially undesirable effects of genetic screening. As one commentator had put it: ‘such effects will be minimized if screening programmes adopt the specific goal, not of reducing the incidence of disease, but of maximizing options available to couples at risk for an affected child’. The task of ethical policy, then, was to reconcile the tensions between individual autonomy and the collective goals of public health. The best way of maximizing autonomy was combining information-giving with psychosocial support to enable individuals to choose wisely. In addition to formulating principles or conducting case-by-case analysis, ethical reasoning within biomedicine had also
developed in relation to particular diseases, a prominent example of which is the development of ethical frameworks for HD.

**HD and ethical reasoning**

HD is a progressive and incurable disorder of the central nervous system dominantly transmitted through an autosomal gene with complete penetrance.\(^2\) In many ways, HD provided an ideal exemplar for organizing ethical reasoning along three important dimensions: severity of the disease, mode of inheritance and availability of treatment. Prior to discovering the approximate location of a causal gene in 1983,\(^2\) a discourse on the ethical issues of counseling families at risk of HD had existed since the early 1970s.\(^2\),\(^3\) However, after 1983, ethical concerns over predictive testing on presymptomatic adults and children had undergone intense discussion and debate.\(^2\),\(^3\) Some believed that predictive testing might be used to postpone reproductive decisions, while others preferred the withdrawal of testing until a treatment or cure was found.\(^2\) The high premium placed on individual autonomy also meant that issues of childhood testing generated tensions between the rights and capacities of minors and the rights and responsibilities of parents.\(^2\),\(^3\) By the time a precise location of the gene was isolated,\(^2\) the ethical, legal and psychosocial aspects of HD had been subject to intense investigation.

In light of the perceived fears about psychosocial implications of testing for HD, the professional community proceeded very cautiously. Studies of psychiatric morbidity seem to confirm that receiving an early diagnosis may result in suicide and depression,\(^3\),\(^5\) while others reported problems of confidentiality, legal protection and informed consent.\(^5\),\(^7\)–\(^3\) However, these early fears about genetic testing were counterbalanced by surveys indicating that lay people held positive attitudes and consistently endorsed such testing even in the absence of an effective cure.\(^4\),\(^5\) Guidelines were established by the World Federation of Neurology along with the International Huntington’s Association and the UK Huntington’s Disease Prediction Consortium.\(^4\),\(^5\) Too numerous to quote in full,\(^5\) the guidelines can be summarized as follows:

- The decision to take the test should be voluntary, free of coercion and based on informed consent.
- No test should be offered without proper counseling and professional support.
- The test should only be available to those who have reached the age of majority.
• No person should be discriminated against as a result of testing.
• Testing should be delayed if there is evidence that the results will lead to psychosocial harm.
• The results of a test are confidential and the property of the individual, and under no circumstances shall any professional communicate this information to third parties.

These and other variations of the guidelines bear more than a passing resemblance to the four bioethical principles of autonomy, beneficence, non-maleficence and justice. In a succinct statement of the ethical concerns faced by families, one experienced practitioner described HD as a ‘paradigm of testing’: ‘The test for the HD gene raises critical issues with respect to the right of people to know genetic information, their right not to know and the right of privacy for minors’.46

While many stand to benefit from guidelines on predictive testing for HD, the formulation of ethical frameworks in terms of principles and exemplars are not without criticism. The common expectation among ethicists and health professionals is that robust frameworks can serve as guidelines for the genetic testing of other conditions.37,38 However, some have complained whether the complexity of the ethical dilemmas that families and professionals face in the clinic can be reduced to abstract principles.47 Evans has noted that principlism in bioethics is ‘a method that takes the complexity of actually lived moral life and translates this information into four scales by discarding information that resists translation’.48 Furthermore, Boddington and Hogben49 have argued that using HD as a specific disease exemplar for genetic policy stresses ‘a difference in degree of seriousness’ which ‘translates into a substantive difference of kind in justifying ethical argument’. In other words, selecting the severity of a condition to make an ethical argument implies that all genetic conditions can be compared quantitatively rather than qualitatively. Boddington and Hogben speculate whether the selection of other candidate conditions may have led to different policy conclusions. Indeed, it is worth asking: to what extent has HD informed ethical policy on other kinds of genetic conditions with different attributes of severity, treatability and inheritance?

The rest of the paper will consider whether such quantitative arguments are sufficient to deal with the social–ethical implications of susceptibility testing for Alzheimer’s disease (AD). My point is that HD may not be the best exemplar to construct ethical arguments for susceptibility testing in general, and that we may need to develop new arguments by considering alternative disease exemplars. The case is made that AD provides a way of thinking about the impact and validity of genetic risk in ways that predictive testing for HD do not. AD illustrates that ethical reasoning may vary qualitatively in terms of the
‘genetic complexity’ of a condition, which places emphasis not on its presumed severity but on the communication and interpretation of risk. Communication of complex risk plays a much more important role in shaping the psychological and behavioural impact of genetic susceptibility testing.

Genetic testing for Alzheimer’s

In the last 20 years, there has been consensus among researchers that rare autosomal dominant genes are strongly associated with the ‘early onset’ form of dementia. However, in 1993 the apolipoprotein E (APOE) ε4 allele on chromosome 19 was found to be associated with an increased risk for the common ‘late onset’ form of AD. The presence of ε4 increases risk of AD up to 15-fold compared with other APOE polymorphisms. The aetiology of AD shows that susceptibility testing is different from predictive testing in that risk information is relevant to a much larger population but is much less certain than predictive testing. Given that there are no treatment options for AD, professionals have cautioned against the routinization of susceptibility testing in presymptomatic individuals.

This resembles the ethical position adopted in relation to HD. In fact, the comparison with HD was common among ethical discussions around genetic testing for AD and was explicitly proposed as an ethical model for other late onset disorders. In this sense, susceptibility and predictive testing are ethically similar if ‘ethical principles’ and ‘disease exemplars’ are used as benchmarks for discussion. This style of ethical reasoning may well be justified if the comparison was between HD and the early onset form of AD. However, APOE4 is characterized as a ‘susceptibility’ gene, conferring only small to moderate risk, and further modulated by environmental factors. Thus, the two conditions differ substantially in terms of inheritance and penetrance. To put it simply, unlike HD, testing positive for APOE4 cannot tell you whether someone is going to develop AD.

In light of these differences, it is curious that APOE testing should be subject to the same ethical control as predictive testing for HD. Hedgecoe argues that the reasons for this were established early on. Between 1994 and 1997, seven consensus conferences were held to establish a viewpoint on whether APOE should be used for diagnostic testing of AD. Even though the 1997 meeting deemed APOE testing ‘clinically relevant’, five conferences (one conference reached an equivocal conclusion) claimed that APOE testing was not appropriate given that sensitivity and specificity figures were too low to be clinically useful. However, it was not a scientific argument but an ethical one...
that seem to have the most impact on the professional community. The ‘burden of testing’ argument claimed that APOE genotyping was ‘ripe for misunderstanding’ among families and increased ‘social cost and psychological burdens’. In a statement indicative of professional skepticism, justification against APOE testing was based on the ‘foreseeable, significant psychosocial consequences for family members that must be weighed against any hypothetical psychosocial benefits associated with a modest increase in diagnostic certainty’. However, given that there was no empirical support at the time to suggest that diagnostic testing was harmful, we can only assume that McConnell and colleagues claim ‘foreseeable’ and ‘significant’ psychosocial consequences based on early concerns about HD testing. Indeed, as later research has shown (see below), it is not clear at all that people identified with carrying APOE4 show foreseeable and significant psychosocial distress.

The debate over whether clinicians should use APOE4 testing runs much deeper than the psychosocial argument. Advocates of APOE claim that testing may be useful when it is used as a ‘diagnostic adjunct’ if a patient presents with symptoms of dementia, then the test may help determine what kind of dementia the patient is suffering from. However, a deeper concern that runs through the professional community is the uncertainty involved in the interpretation of APOE4 results. While AD experts may accept that carrying one copy of the APOE4 allele increases lifetime risk by a modest amount, they are more concerned about what this information would mean to not only patients and their families but also physicians. The probabilistic nature of susceptibility is notoriously difficult even for physicians to understand. Erring on the side of caution, then, professionals have employed ethical arguments to regulate the clinical use of APOE testing.

A number of developments have occurred recently which make the APOE debate an important case for reconsidering ethical frameworks for susceptibility testing. As the cost of genotyping and sequencing becomes significantly cheaper, the number of genetic tests for susceptibility is likely to increase and is likely to place additional pressure on state provided health-care systems to offer such tests in the future. A relevant concern for ethical discussion is not only the evaluation and regulation of such tests, but the need for empirical analysis to measure and evaluate the effect these tests have on behaviour. The issue of behaviour change is more central to susceptibility testing where there is a presumption that some kind of lifestyle modification may reduce the risk of disease. In the case of HD testing, this possibility is ruled out—no amount of behaviour change will alter the fate of those who test positive—and yet people may want to know their risk for different reasons: to plan their future, to consider their reproductive choices or
to know their children’s risk. For families at risk of AD, or who carry the APOE risk allele, the benefits of susceptibility testing are much less certain. How do people act on information that is probabilistic and weakly predictive? Would a positive test result motivate behaviour change? Existing ethical frameworks that rely on the presumed resemblance to HD are likely to be unhelpful, because the psychosocial argument does not come to grips with the issue of how people react to and understand highly probabilistic risk information.

As it stands, there are five major areas in which the effects of complex genetic information have been studied: cancer, heart disease, diabetes, smoking and AD. In the last section, I briefly review the first major study to assess the psychological and behavioural impact of susceptibility testing for AD. The findings of this study are important because they confirm that the ethical implications of such testing are qualitatively different from the kind of psychosocial distress that may occur after receiving deterministic risk information (‘yes’ or ‘no’). The ethics of disclosing a genetic diagnosis of susceptibility is contingent on whether professionals accept that probabilistic risk information is in fact ‘diagnostic’ and on an empirical understanding of how people actually perceive, recall and comprehend complex risk information.

The REVEAL study

The REVEAL study (Risk Evaluation and Education for AD) was the first randomized controlled trial designed to evaluate the impact of susceptibility testing using APOE4. The study was conducted at four sites in the USA between 2004 and 2006. At one site, 162 asymptomatic adults who had an affected parent were randomly assigned to either receive susceptibility testing or not receive susceptibility testing. Both groups were measured for symptoms of anxiety, depression and test-related distress 6 weeks, 6 months and 1 year after (non) disclosure. The results showed no significant differences between the two groups, though those who received a negative result showed significantly lower levels of test-related distress than did the positive group.

A separate study compared the results of the REVEAL subjects with those who received monogenetic testing; subjects who learned that they were positive for the susceptibility gene experienced similar low levels of distress compared with those who tested positive for the monogenetic test. They also found that ‘both susceptibility and deterministic genetic testing appeared to be well tolerated by using disclosure protocols that provided screening, education, counselling and follow-up’. In the ethnographic arm of the study, Locke et al.
raised questions about the relevance and comprehension of testing. They suggested that the pressures of daily life and care-giving, and the combined uncertainty of the genetic information, encouraged a high proportion of their sample to ‘set aside’ or forget their future risk. In a follow-up study, the REVEAL participants who tested positive for APOE4 were significantly more likely to report health behaviour changes, ‘even if the effectiveness of the activities [were] uncertain’. It is worth noting, however, that the study participants were predominantly female, white and college educated and had voluntarily sought genetic testing.

We can draw a number of inferences from this preliminary data. It is widely recognized that epidemiological information has a small impact on risk perception because probabilistic information is not meaningful to families. They often simplify or condense complex information by translating risk and uncertainty to a binary form or to a descriptive category. In people’s accounts of genetic risk, ideas about genetics and heredity are often fused, which is sometimes viewed as a misunderstanding of science, but an alternative explanation is that conflation is a lay strategy of comprehension to render complex information more concrete and familiar. Furthermore, notions of genetic susceptibility are quite similar to lay explanations of misfortune, liability and risk. People have pre-existing and well-developed models of predisposition or vulnerability, which are mitigated or aggravated by personal and environmental factors. Rather than perceiving risk estimation for AD as deterministic and ‘genetically exceptional’, people are likely to incorporate this information within existing models of multifactorial causation. This may account for the resilience, and perhaps even the skepticism, with which risk estimates were regarded in the REVEAL study.

Table 1 provides an illustrative comparison between predictive testing for HD and susceptibility testing for AD. In the case of predictive testing for Mendelian disorders, the low complexity of information coupled with the genetically exceptional nature of the test produces high impact of risk perception and low recall error. For susceptibility testing for complex disorders, the high complexity of information coupled with information about lifestyle are likely to dampen the impact of risk perception, resulting in high recall error. This was confirmed by at least one set of findings in the REVEAL study where only 27% of participants recalled their test results accurately, while 23% were unable to recall their genotype or risk estimates at all. It is a well-known feature of risk perception that the characteristics that impress themselves more strongly on perception are those which are linked to dread or which are already familiar to people. While there is a modicum of evidence to suggest that knowledge of increased risk
for AD may lead to behavioural change, there is no empirical evidence at this stage to suggest that susceptibility testing is psychosocially harmful. The REVEAL study confirms that receiving a positive result for either the rare or the common gene is ‘well tolerated’ when disclosure is mediated by genetic counselling.

**Conclusion**

Historically, guidelines and policies for regulating the use of genetic testing for HD have drawn on bioethical principles to protect the autonomy and privacy of individuals and families, much of which has been justifiably concerned about the psychological impact of predictive testing. HD has been used as a dominant case to translate these principles to other kinds of genetic testing. And while this may be an expedient way of formulating ethical policy, placing genetic disorders along a continuum of severity excludes the qualitative distinction between ‘simple’ and ‘complex’ genetics. Conditions characterized by their genetic complexity are not reduced ethically in terms of their severity but require a different set of responsibilities in terms of explaining and discussing the weakly predictive value of a susceptibility-conferring risk allele. The issue here is that protecting the autonomy of individuals...
before they seek a test may not be as important as discussing what the results mean. Understanding whether the results are meaningful is an issue that will need to be negotiated between professionals and individuals, it will require frank discussions about the interpretation of complex risk, the degree to which people can or should modify their lifestyles and whether they should take prophylactic medications.

The new evidence that has come to light on the effects of receiving a positive or negative result for APOE testing of AD suggests that professionals’ ethical concerns about presumed psychosocial harms are not entirely justified. Furthermore, the modest estimation of risk along with mitigating lifestyle and environmental factors are likely to dampen the effect of risk perception and the priority for behavioural change. The REVEAL study confirms that receiving complex risk information is ‘well tolerated’ by participants who received a positive test result, and that there is no significant difference between those receiving a monogenetic test result (for the early onset form of AD) and those receiving a result for disease susceptibility. This raises a number of implications about the kinds of ethical protocols needed to ensure that complex risk information is offered responsibly. It is not the psychosocial aspects of disclosing genetic risk that is urgent, nor even the relevance of ethical principles to control the use of predictive testing. Rather, the more pressing concern is whether susceptibility testing for common complex diseases produces clinically valid and useful information. The genetic complexity of common diseases casts doubt over whether accurate prediction will ever be possible.

The availability of susceptibility testing for many common diseases, such as AD, is likely to increase in the future. This will require ethical guidelines that focus not on whether the information increases or decreases distress, autonomy or prevention, but whether professionals and families are properly informed about the limits of complex risk information. It is well known that lay perceptions and reactions to genetic tests are mediated by public understandings of genetics as well as clinical presentation of risk information. In the case of genetic susceptibility, there is a greater burden of responsibility to provide accurate interpretation when the prevailing assumption of the public is that genes are immutable and deterministic. This is especially important given that APOE testing is currently available via direct-to-consumer genetic testing companies where, in many cases, there is no obligation to provide genetic counselling. The REVEAL study clearly shows that genetic counselling is an important factor in producing reactions and perceptions to testing that present no cause for alarm. In fact, the results of the study may well have been an artefact of receiving genetic counselling in the first place. However, it is not clear whether genetic counselling services, who are already burdened
with counselling for Mendelian disorders, will want to, or have the
capacity to, take on this responsibility. Nevertheless, a new ethical
paradigm will need to recognize the qualitative distinction between
simple and complex genetic risk, and the different kinds of communi-
cative responsibilities that each entail. For practitioners, this means that
disclosing genetic susceptibility for common complex diseases such as
Alzheimer’s is not the same as offering a diagnosis, but the art of
managing expectations and interpreting risk on a delicate balance of
uncertainties.

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