

GENETICS

Firing up the nature/nurture controversy: bioethics and genetic determinism

I de Melo-Martín

J Med Ethics 2005;31:526–530. doi: 10.1136/jme.2004.008417

Correspondence to:
Dr Inmaculada de Melo-
Martín, Associate
Professor, Department of
Philosophy, St Mary's
University, San Antonio,
TX 78228, USA;
mdemelomartin@
stmarytx.edu

Received 13 February 2004
In revised form
27 August 2004
Accepted for publication
16 November 2004

It is argued here that bioethicists might inadvertently be promoting genetic determinism: the idea that genes alone determine human traits and behaviours. Discussions about genetic testing are used to exemplify how they might be doing so. Quite often bioethicists use clinical cases to support particular moral obligations or rights as if these cases were representative of the kind of information we can acquire about human diseases through genetic testing, when they are not. On other occasions, the clinical cases are presented in simplistic ways that portray genetic testing as yielding information more accurate than it actually is. It is concluded that, because of the problematic implications that the ideology of genetic determinism might have for individuals' wellbeing and for our public policies, bioethicists should be careful to present these issues in ways that do not promote questionable ideas about the causal role of genes in human diseases and behaviours.

Discussions of genetic determinism, the idea that genes alone determine human traits and behaviours, have been around for a long time. So much so, that some have suggested that arguing against genetic determinism is like battling the undead: no matter how many times you stab them, they keep coming at you.¹ This is the case despite practically every geneticist alive having disavowed genetic determinism. Psychologist Susan Oyama has argued that genetic determinism is inherent in the way we represent what genes do. Genes are given a privileged causal status. They are thought to cause development in a way fundamentally different from all the other material factors known to be involved. Equal recognition is not being given for equal work. Thus today's "interactionist" talk, far from debunking genetic determinism, simply reinforces it, because genes are still represented as containing information about how the organism will develop. Hence some have suggested that finding a new way to think about genes is a necessary prerequisite to putting a "stake in the heart" of the nature/nurture controversy.^{2,3}

Just as those who work in the field of genetics might inadvertently be promoting the ideology of genetic determinism, bioethicists working on the ethical, legal, and social implications of genetic technologies might be doing the same. In part they might do so by assuming the correctness of the framework used to represent what genes do. The purpose of this paper, however, is to argue that bioethicists might be promoting genetic determinism by other, albeit related, means. They might do so because quite often the cases they use to support particular ethical claims suggest that the genes play a more central role in human development, disease, and behaviour, than they might actually do. For instance, the flood of arguments against human cloning on grounds of a possible loss of a sense of individuality or unique identity promote the incorrect belief that our genes determine human individuality or identity.^{4–7} Similarly, many of the debates about the rightness or wrongness of genetic enhancement,^{8,9} erroneously suggest that tinkering with the human genome is sufficient to "enhance" our memory, intelligence, disease resistance, or beauty. In other cases, bioethicists present

genetic tests as being more predictive of human diseases than what is actually reasonable.

Although there are a variety of instances where bioethicists' discussions of genetic technologies might promote genetic determinism, I will focus here on just one of them: the case of genetic testing and the presumed moral obligations that follow from our newly found ability to obtain genetic knowledge about ourselves and others.¹⁰ Here, this promotion of genetic determinism results from the use of clinical cases to support particular moral duties. Although on these occasions the predictive power of genetic testing is presented in a more or less correct way, the clinical cases are offered as if they were representative of the kind of information we can acquire about human disease through genetic testing when, actually, they are not. Moreover, genetic determinism might be promoted because the clinical cases are presented in simplistic ways. This simplification, however, portrays genetic testing as yielding information more accurate than it actually is. Thus, again, genetic information is presented in a way that erroneously indicates that genes are the primary factors in the development of human diseases.

I use the debate on genetic information and the moral obligations that presumably result from them for two main reasons. First, these debates have received wide attention in the bioethics literature. Second, because unlike—for example, human cloning or enhancement—genetic testing is an actual and increasingly common medical technology. Thus, discussions related to them are more salient for our present circumstances.

Promoting genetic determinism is problematic for several reasons. First, there is no empirical foundation for the belief that genes alone determine most human traits and behaviours. This is not to say that genes play no role at all, nor to reject the claim that sometimes genes might provide the best explanation for the genesis of a trait. To reject genetic determinism is simply to reject the idea that genes alone play

Abbreviations: BAPP, beta-amyloid precursor protein; APOE, apolipoprotein E

a role in the development of human traits and behaviours. Second, promoting genetic determinism is problematic because it can contribute to public policies that emphasise genetic interventions rather than preventive measures, lifestyle modifications, or transformations of social structures. If, however, factors other than our genes influence the development of—for example, human diseases—then focusing on genetic interventions alone will be inefficient. Third, the belief that genes determine us might result in people seeing information about their genetic make up as fate. Thus, although lifestyle changes could improve people's wellbeing, the motivation to do so might be lacking.

Note that my point here is not to argue that bioethicists or scientists do believe genetic determinism to be correct. On the contrary most have been very concerned with trying to show that genetic determinism is not just false, but also dangerous. My point is to call attention to common practices that might keep throwing fuel onto the fire of the nature/nurture debate. Intellectual honesty and care for the human community require that we pay careful attention to this issue.

UNREPRESENTATIVE CASES

A number of authors have used Huntington's disease and Tay Sachs to illustrate the kinds of distinct issues involved in ethical decisions that result from our ability to obtain genetic information about our children and ourselves.^{10–15} Thus, these authors have maintained that under certain circumstances—for example, those present when we are at risk of suffering or transmitting to our offspring diseases such as Huntington's and Tay Sachs—we have a duty to know about those hereditary disorders, an obligation to inform those members of our family that might also be at risk of carrying those harmful genetic mutations, and a duty to try not to bring affected babies into this world. Of course, Huntington's disease and Tay Sachs are not the only serious genetic diseases about which we can acquire knowledge through genetic analysis. These diseases are, however, seen as particularly useful in supporting moral duties to use genetic information for reproductive purposes and in supporting moral obligations to obtain and disclose such information. This is so because the predictive value provided by genetic testing for Huntington's disease and Tay Sachs is quite high. Hence, these important ethical issues hinge on our ability to obtain accurate genetic knowledge about others and ourselves.

Huntington's disease is due to a mutation in a gene that is transmitted as an autosomal dominant trait.^{16–21} Each child of a parent who is carrying a mutated allele for Huntington's disease has a 50% risk of inheriting the gene. The child needs only one copy of the gene from either parent to develop the disease. A person who inherits the Huntington's disease gene, and survives long enough, will sooner or later develop the disease. If the child does not inherit the defective gene, it is unlikely that the child will either get the disease or pass it on to subsequent generations. In most cases, the Huntington's disease gene is thought to have 100% penetrance.^{22–23}

Tay Sachs has a different mode of inheritance.^{24–27} This disease is inherited in an autosomal recessive pattern, which means two copies of the gene must be altered for a person to be affected by the disorder. Most often, the parents of a child with an autosomal recessive disorder are not affected, but are carriers of one copy of the altered gene. They have a 50% chance of passing on the mutated gene to their children. A child who inherits one inactive gene is a Tay Sachs carrier like the parent. If both parents are carriers and their child inherits the mutated gene from each of them, the child will have Tay Sachs disease. When both parents are carriers, each child has

a 25% chance of having Tay Sachs disease and a 50% chance of being a carrier.

Because Tay Sachs disease is very rare in the general population,^{28–30} authors using Tay Sachs as their clinical case to support claims about particular moral obligations tend to present the case in the context of communities that have a significant number of Tay Sachs carriers. That is the case for the Ashkenazi Jewish population (Jews of Central or Eastern European descent), in which the disease incidence is one in every 3500 newborns: approximately 100 times higher than in the general population. Among Ashkenazi Jews, one in every 29 individuals is heterozygous, and thus asymptomatic, for Tay Sachs disease causing mutations. The current tests detect about 95% of carriers of Ashkenazi Jewish background. Thus, the predictive power of the test for Ashkenazi Jews is quite high.

The problem with these cases, and the reason why bioethicists using them might inadvertently promote genetic determinism, is that they are unrepresentative of the kind of information that we can, and presumably will be able to, obtain for the majority of diseases with a genetic component that might affect most human beings.^{31–33} Diseases such as cancer, heart problems, diabetes, and mental disorders are much more difficult to predict accurately than are rare Mendelian diseases such as Huntington's or Tay Sachs—that is, diseases that are caused by a single mutated gene. This is so, because alleles conferring susceptibility or resistance to complex or multifactorial diseases lack the deterministic nature of single gene mutations. Alleles contributing to complex diseases might be neither necessary nor sufficient to cause the particular disease. In many cases, more than two loci might contribute to the disease, and those loci might interact with each other. Depending on their roles in the pathogenesis of diseases, these interactions might be additive, multiplicative, or might have no additional effect. Also, the effects of interaction of a susceptibility allele with a protective allele might be especially difficult to predict with any accuracy. Moreover, the expression of most human diseases involves the relations of multiple genetic and environmental factors. Furthermore, cases of incomplete penetrance and variable expressivity introduce difficulties in our ability to obtain accurate information about the risks of developing a particular disease.^{32–35} Even in cases of so called monogenetic diseases such as phenylketonuria and cystic fibrosis, it is difficult to predict how the mutant genotype is going to affect the severity of the disease.^{36–38}

The use of unrepresentative cases when discussing genetic testing and moral obligations might foster in the general public the idea that genetic information is usually highly predictive of disease. This is especially the case when there is no mention in these discussions that the predictive power of tests for Huntington's and Tay Sachs is atypical. The use of these cases might help support inadequate perceptions about the causal role of genes in human diseases. This inadequate perception might in turn contribute to the development of public policies that promote the use of unnecessary genetic testing and screening, preimplantation diagnoses, or genetic selection of embryos for complex disorders, and the limitation of research efforts aimed at primary prevention. Similarly, the idea that genes are the main contributors to human diseases could encourage a lack of individual self care. Already, some studies indicate that individuals found to be at risk of heart disease through the use of a genetic test may feel the development of the disease is inevitable and there is less that can be done about it than when the risk is based on other clinical tests.^{39–40}

Some might object that although currently tests for genetic conditions might not be highly predictive of whether someone is going to develop a particular disease, this might

be due to the fact that we do not have sufficient knowledge. Presumably they suppose that research on multifactorial diseases would allow us to produce accurate tests. This objection is, however, problematic because it presupposes that our genes alone are the cause of phenotypic traits. As mentioned earlier, however, we have no empirical evidence supporting this presupposition. This is not to say that complex and common diseases and disorders have no genetic component whatsoever. It is only to point out that because of the complex interactions between genes with other genes and with their environments, the predictive power provided by genetic tests might be too low to have important medical and social applications. Genetic tests can only give us information about one of the many parts playing a role in the system. So even if they are highly reliable on the information about the genetic component, they still cannot give us much information about developmental interactions or the role of the environment.

Bioethicists using these cases could also object that it is not their fault that people interpret such cases as being representative of the kind of predictability that we can gain from genetic testing. This objection, however, is far from compelling. The debates are centred on the issue of what moral obligations we have to ourselves and to others by virtue of our ability to obtain genetic knowledge. It would then seem odd to make claims about moral obligations by which all human beings are presumably bound, when we are referring only to a very small section of the human community. Thus, reasonable people might be led to assume incorrectly that the reliability of the information for Huntington's and Tay Sachs is representative of the kind of information we can obtain about genetic diseases that affect human beings. Moreover, even if these authors want to argue that actually these moral obligations would affect a very small percentage of the population, they should say so. We cannot forget the social context in which we are discussing these issues. We have abundant historical evidence that shows the eagerness of governments and their citizens to use information about genetics in order to promote oppressive public policies.

SIMPLIFIED CASES

Presenting clinical cases of monogenetic diseases for which we have highly predictive tests as if they were representative cases is not the only way in which bioethicists dealing with genetic testing might be promoting genetic determinism. A different way appears when information about diseases with a genetic component and the predictability of genetic tests for these diseases is presented in simplistic ways.

Two of the diseases often used in this way are Alzheimer's disease and cancer, specifically breast cancer.^{13 41 42} As in the cases discussed earlier, bioethicists use these diseases in the context of arguing for particular moral obligations we might have to others and to ourselves. As before, genetic testing is the tool used to obtain information about these genetic conditions. We are thus informed that testing for genetic mutations in breast cancer and Alzheimer's is available and that having such genetic mutations puts people at an increased risk of suffering the disease. In some cases we might be told that in the case of breast cancer, two main mutations have been found in the BRCA1 and BRCA2 genes, which entail a significantly high risk of breast (between 50% to 85%) and ovarian (up to 60%) cancer over a lifetime. Also, we are often informed that, as a dominant disorder, children of people with these mutations have a 50% chance of carrying the mutation. Sometimes we might also be informed that these mutations account only for about 5–10% of all breast cancers. In the case of Alzheimer's disease we might be informed that a mutation in the gene for beta-amyloid

precursor protein (BAPP) when combined with apolipoprotein E (APOE) has been implicated as a cause of Alzheimer's disease. People with the BAPP mutation and the e4 allele of APOE develop Alzheimer's much earlier than those with BAPP and other alleles of APOE. People with two copies of the APOE4 have about a 90% chance of eventually developing the disease. In some cases, we are simply told that genetic testing for mutations for breast cancer and for Alzheimer's exist. As before, the predictive power of these genetic tests is quite relevant, if not essential, for the arguments offered.

Presented in this way, we might get the impression that the predictive power of genetic tests for these conditions is quite high, and thus that the genetic information is highly predictive of the development of these diseases: but this impression would be erroneous. Let us begin with the breast cancer case.^{44–49} BRCA1 and BRCA2 have been identified as two of the genes associated with hereditary breast and ovarian cancer. This constitutes only 5–10% of all breast and ovarian cancers. Thus far, more than 200 different specific mutations have been described in the two BRCA genes. Some of these mutations seem to be more prevalent in particular ethnic groups. Moreover, the gene penetrance varies with the particular mutations, and this has an impact on our ability to accurately estimate cancer risks. Also, it is important to point out that the information available at present is entirely derived from very high risk families, and the possible gene penetrance in different contexts is unknown. The reliability of BRCA screening depends on prior probability of the condition, sensitivity and specificity, screening techniques, and number of mutations.

As for Alzheimer's disease, studies have documented the presence of autosomal dominant mutations on chromosomes 1, 14, and 21 in families with Alzheimer's affected individuals, and genetic tests have been developed to test for these mutations.^{51–56} Because, however, these mutations are quite likely not the only mutations influencing Alzheimer's disease, the meaning of a negative test result is of limited predictive use. On the other hand, a positive result must be interpreted in light of the effect of variable gene expression and incomplete penetrance on the disease development and severity. Together, these facts point to limits in the predictability of tests for disease producing mutations. Similarly, although the presence of the APOE e4 allele is associated with a higher risk and decreased age of onset of Alzheimer's disease, the absolute magnitude of the risk is difficult to assess. This is so, because the risks vary as a function of age, gender, ethnicity, exposure to toxins, head trauma, and other susceptibility genes. Thus, even when the test correctly reveals the presence of mutations related to Alzheimer's disease, it does not do a good job of predicting who will get the disease. A substantial proportion of APOE e4 carriers, including those surviving into the 10th decade, do not become demented; while more than one third of persons with Alzheimer's disease do not have the e4 allele. Studies have shown that the rate of false positives and false negatives are quite high. Thus, 71% of individuals with one or two APOE e4 alleles never develop Alzheimer's disease and 44% of people with the disease do not have the APOE e4 allele.³²

These cases seem to be more representative of the difficulties faced when dealing with complex genetic traits and thus of the kind of information that genetic testing might be able to offer. Unfortunately, by presenting the cases in simplistic ways, the authors might help maintain mistaken perceptions about the unavailability of all diseases and disorders that might have a genetic component. The simplification of these cases might contribute to incorrect public beliefs about genetic determinism.

Someone might object that using these simplified clinical cases when trying to argue for particular moral obligations is

justified because the point of the discussion is to encourage reflection on significant moral issues such as rights and duties in relation to genetic information, not to present comprehensive scientific knowledge. Of course, my arguments here are not intended to require that complete scientific information be presented in all discussions on ethical issues related to genetics. Such information might be unnecessary in many situations. Even when arguing for particular ethical claims in relation to genetic information one might not need to present all information available about the difficulties of obtaining reliable data from genetic tests. It does not, however, seem unreasonable to request that highly inaccurate information not be given. In some cases, it might be sufficient to simply advise readers that the cases are being presented in simplified ways and to emphasise the fact that many factors, not just our genetic make up, affect the development and severity of most common human diseases.

CONCLUSION

We live in the era of genetics. Genetic science, genetic technologies, genetically based diseases, animal and human cloning, and the hopeful (or frightening) possibility of designer babies are regular visitors to the news and entertainment culture. Together with the revolution in information technologies, and sometimes going hand in hand with it, the biotech revolution promises to transform our world. In many cases, discussions about genetic technologies and genetic information are presented in ways that suggest the predictive ability of genetic analysis is higher than it actually is. This might support ideologies of genetic determinism. Thus, to the extent that we believe that genetic determinism is not just false but highly problematic, bioethicists need to be careful not to present ethical discussions in ways that might promote it.

Also, the arguments presented here are not intended to defend the position that genetic testing is never useful, that it should not be used, or that the predictive value of current genetic tests for complex diseases will never be improved. I have used the case of genetic testing and the presumed moral obligations it might engender as an illustration of how bioethicists might inadvertently promote the ideology of genetic determinism. Hence, my point here has been that bioethicists should be careful to present these and other similar issues in ways that do not promote problematic ideas about the deterministic role of genes in human development, diseases, and behaviours.

ACKNOWLEDGEMENTS

Thank you to Gonzalo Múnevar, Craig Hanks, Adrian Viens, and an anonymous reviewer for helpful suggestions on improving this paper.

REFERENCES

- Oyama S. *Ontogeny of information: developmental systems and evolution*. Cambridge: Cambridge University Press, 1985:26–7.
- Oyama S. Terms in tension: what do you do when all the good words are taken? In: Oyama, S, Griffiths P, Gray R, eds. *Cycles of contingency*. Cambridge: The MIT Press, 2001:177–93.
- Griffiths P. The fearless vampire conservator. In: Rehmann-Sutter C, Neumann-Held E, eds. *Genes in development. Rereading the molecular paradigm*. Durham, NC: Duke University Press, (in press). Reprint available at http://philsci-archive.pitt.edu/archive/00000728/00/Fearless_Vampire_Con servator.PDF (accessed 3 Dec 2004).
- Kass L. The wisdom of repugnance. In: Pence G, ed. *Flesh of my flesh*. Lanham, MD: Rowman and Littlefield, 1998:13–37.
- US National Bioethics Advisory Commission. *Cloning human beings: report and Recommendations of the National Bioethics Advisory Commission*. Rockville, MD: US National Bioethics Advisory Commission, 1997.
- Verhey AD. Cloning: revisiting an old debate. *Kennedy Inst Ethics J* 1994;4:227–34.
- Callahan D. Perspective on cloning: a threat to individual uniqueness. *Los Angeles Times* 1993 Nov 12:B7.
- Juengst E. Can enhancement be distinguished from prevention in genetic medicine? *J Med Philosophy* 1997;22:125–42.
- Glover J. *What sort of people should there be?* New York: Penguin, 1984.
- Rhodes R. Genetic links, family ties, and social bonds: rights and responsibilities in the face of genetic knowledge. *J Med Philosophy* 1998;23:10–30.
- Robertson S, Savulescu J. Is there a case in favour of predictive genetic testing in young children? *Bioethics* 2001;15:26–49.
- Ross LF, Moon MR. Ethical issues on genetic testing of children. *Arch Pediatr Adolesc Med* 2000;154:873–9.
- Buchanan A, Brock DW, Daniels N, et al. *From chance to choice*. Cambridge: Cambridge University Press, 2000:ch 6.
- Cohen CB. Wrestling with the future: should we test children for adult-onset genetic conditions? *Kennedy Inst Ethics J* 1998;8:111–30.
- Purdy L. Genetics and reproductive risk: can having children be immoral? In: *Reproducing persons: issues in feminist bioethics*. Ithaca, NY: Cornell University Press, 1996:39–49.
- MacDonald ME, Gines S, Gusella JF, et al. Huntington's disease. *Neuromolecular Med* 2003;4:7–20.
- Ho LW, Carmichael J, Swartz J, et al. The molecular biology of Huntington's disease. *Psychol Med* 2001;31:3–14.
- Davies S, Ramsden DB. Huntington's disease. *Mol Pathol* 2001;54:409–13.
- Wellington CL, Brinkman RR, O'Kusky JR, et al. Toward understanding the molecular pathology of Huntington's disease. *Brain Pathol* 1997;7:979–1002.
- Wexler A. *Mapping fate*. Berkeley, CA: University of California Press, 1996.
- Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* 1993;72:971–83.
- Holzmann C, Schmidt T, Thiel G, et al. Functional characterization of the human Huntington's disease gene promoter. *Brain Res Mol Brain Res* 2001;92:85–97.
- Durr A, Dode C, Hahn V, et al. Diagnosis of "sporadic" Huntington's disease. *J Neurol Sci* 1995;129:51–5.
- Risch N. Molecular epidemiology of Tay Sachs disease. *Adv Genet* 2001;44:233–52.
- Rozenberg R, Pereira LD. The frequency of Tay Sachs disease causing mutations in the Brazilian Jewish population justifies a carrier screening program. *Sao Paulo Med J* 2001;119:146–9.
- Peleg I, Karpati M, Gazit E, et al. Mutations of the hexosaminidase A gene in Ashkenazi and non-Ashkenazi Jews. *Biochem Med Metab Biol* 1994;52:22–6.
- Yamanaka S, Johnson ON, Norflus F, et al. Structure and expression of the mouse B-hexosaminidase genes, hexa and hexb. *Genomics* 1994;21:588–96.
- Sutton VR. Tay Sachs disease screening and counseling families at risk for metabolic disease. *Obstet Gynecol Clin North Am* 2002;29:287–96.
- Zinberg RE, Kornreich R, Edelmann L, et al. Prenatal genetic screening in the Ashkenazi Jewish population. *Clin Perinatol* 2001;28:367–82.
- Petersen GM, Rotter JL, Cantor RM, et al. The Tay Sachs disease gene in North American Jewish populations: geographic variations and origins. *Am J Hum Genet* 1983;35:1258–69.
- Cummings M. *Human heredity: principles and issues* [6th ed]. Pacific Grove, CA: Brooks/Cole, 2003:ch 5.
- Wilkie A. Genetic prediction: what are the limits? *Stud Hist Phil Biol & Biomed Sci* 2001;32:619–33.
- Risch NJ. Searching for genetic determinants in the new millennium. *Nature* 2000;405:847–56.
- Dennis C. Epigenetics and disease: altered states. *Nature* 2003;421:686–9.
- Vineis P, Schulte P, McMichael AJ. Misconceptions about the use of genetic tests in populations. *Lancet* 2001;357:709–12.
- Dipple KM, McCabe ER. Phenotypes of patients with "simple" Mendelian disorders are complex traits: thresholds, modifiers, and systems dynamics. *Am J Hum Genet* 2000;66:1729–35.
- Mickle JE, Cutting GR. Genotype-phenotype relationships in cystic fibrosis. *Med Clin North Am* 2000;84:597–607.
- Scriver CR, Waters PJ. Monogenetic traits are not simple. Lessons from phenylketonuria. *Trends Genet* 1999;15:267–72.
- Senior V, Marteau TM, Weinman J. Impact of genetic testing on causal models of heart disease and arthritis: an analogue study. *Psychol Health* 2000;14:1077–88.
- Senior V, Marteau TM, Peters TJ. Will genetic testing for predisposition for disease result in fatalism? A qualitative study of parents' responses to neonatal screening for familial hypercholesterolaemia. *Soc Sci Med* 1999;48:1857–60.
- Glannon W. *Genes and future people*. Boulder, CO: Westview, 2001.
- Wachbroit R. The question not asked: the challenge of pleiotropic genetic tests. *Kennedy Inst Ethics J* 1998;8:131–44.
- Khabele D, Runowicz CD. Genetic counseling, testing, and screening for breast and ovarian cancer: practical and social considerations. *Curr Womens Health Rep* 2002;2:163–9.
- Coughlin MJ, Khoury SS, Steinberg KK. BRCA1 and BRCA2 gene mutations and risk of breast cancer: public health perspectives. *Am J Prev Med* 1999;16:91–8.
- Weitzel JN. The current social, political, and medical role of genetic testing in familial breast and ovarian carcinomas. *Curr Opin Obstet Gynecol* 1999;11:65–70.
- Garber J. A 40 year old woman with a strong family history of breast cancer. *JAMA* 1999;282:1953–60.
- Hopper JL, Southey MC, Dite GS, et al. Population based estimate of the average age specific cumulative risk of breast cancer for a defined set of protein truncating mutations in BRCA1 and BRCA2. Australian Breast Cancer Family Study. *Cancer Epidemiol Biomarkers Prev* 1999;8:741–7.

- 48 **Ford D**, Easton DF, Stratton M, *et al*. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. *Am J Hum Genet* 1998;**62**:676–89.
- 49 **Collins FS**. BRCA1—lots of mutations, lots of dilemmas. *N Engl J Med* 1996;**334**:186–8.
- 50 **Shadlen MF**, McCormick WC, Larson EB. Research agenda for understanding Alzheimer disease in diverse populations: work group on cultural diversity, Alzheimer's association. *Alzheimer Dis Assoc Disord* 2002;**16**(suppl 2):96–100S.
- 51 **Green RC**. Risk assessment for Alzheimer's disease with genetic susceptibility testing: has the moment arrived? *Alzheimer's Care Quarterly* 2002;**3**:208–14.
- 52 **Warwick Daw E**, Payami H, Nemens EJ, *et al*. The number of trait loci in late onset Alzheimer's disease. *Am J Hum Genet* 2000;**66**:196–204.
- 53 **Farrer LA**, Cupples LA, Haines JL, *et al*. Effects of age, gender and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: a meta-analysis. *JAMA* 1997;**278**:1349–56.
- 54 **Kahn J**. Ethical issues in genetic testing for Alzheimer's disease. *Geriatrics* 1997;**52**(suppl 2):30–2S.
- 55 **Post SG**, Whitehouse PJ, Binstock RH, *et al*. The clinical introduction of genetic testing for Alzheimer's disease. *JAMA* 1997;**277**:832–6.
- 56 **Bird TD**, Levy-Lahad E, Poorkaj P, *et al*. Wide range in age of onset for chromosome 1 type familial Alzheimer disease. *Ann Neurol* 1996;**40**:932–6.