Clin Genet 2006: 69: 199–203
Printed in Singapore. All rights reserved

CLINICAL GENETICS
doi: 10.1111/j.1399-0004.2006.00581.x

Perspectives

Genetic knowledge and moral responsibility: ambiguity at the interface of genetic research and clinical practice

Pullman D, Hodgkinson K. Genetic knowledge and moral responsibility: ambiguity at the interface of genetic research and clinical practice. Clin Genet 2006: 69: 199–203. © Blackwell Munksgaard, 2006

Despite a rapidly expanding literature on the issue of duty to warn at-risk relatives in the context of clinical genetic testing, little has been written on parallel issues with regard to the management of genetic research results. Some might view this lack as an indication that there is little to discuss in this regard. That is, standard practice is that data obtained through medical research should not be treated as though they are clinically relevant, and this standard should hold for genetic research as well. This paper challenges this conclusion and its underlying assumptions. We argue that the line between genetic research and clinical practice is often ambiguous. In some cases, research data gathered from a very small number of subjects could have immediate clinical implications. Hence, it is unethical for genetic researchers to absolve themselves of clinical responsibilities for research subjects and/or their families, on the grounds that the data were obtained for research purposes. Indeed, we argue that it could well be unethical to embark on some forms of genetic research unless advance arrangements have been made for genetic counseling and clinical follow-up. Furthermore, in some cases, it might be unethical to enroll subjects in studies if the subjects are unwilling to receive their individual results.

D. Pullman[a] and K. Hodgkinson[b]

[a]Medical Ethics, and [b]Patient Research Centre and Discipline of Genetics, Memorial University of Newfoundland, St. John's, Newfoundland and Labrador, Canada A1B 3V6

Key words: genetic research – ethics – duty to warn – privacy

Corresponding author: Dr Daryl Pullman, Associate Professor of Medical Ethics, Memorial University of Newfoundland, St. John's, NL, Canada A1B 3V6.
Tel.: +1 709 777 6220;
fax: +1 709 777 7382;
e-mail: dpullman@mun.ca

Received 30 September 2005, revised and accepted for publication 3 January 2006

Despite a rapidly expanding literature on the issue of duty to warn at-risk relatives in the context of clinical genetic testing, the situation remains ambiguous. Recent commentary tends to favor considerations of individual autonomy, patient confidentiality, and the individual's right to control his or her genetic information (1–3). However, there are those who argue for an evolving 'duty to warn' which may override considerations of patient confidentiality and the right not to know genetic information (4, 5). Some have reframed the debate as a matter of familial obligation with a 'duty to share' clinically relevant genetic results with relatives (6), supported by an emerging 'principle of mutuality' that supersedes individual autonomy in the genetics era (7). Emerging case law in the United States moves to support this principle, as it extends the responsibility of clinicians beyond immediate patients to include family members (8, 9). Meanwhile, broad privacy legislation pushes back in the other direction, as it tends to restrict the sharing of genetic information (1, 10, 11). The predictable result is moral distress for health care professionals (12).

The current focus on the clinical situation with an emphasis on duty to warn fails to address parallel issues with regard to the management of genetic research results (13). On the face of it this lack may appear understandable, as there is a general proscription against sharing individual results in medical research. This is because the validity of clinical trial information is generally cumulative in nature, such that perceived results with a single research subject cannot, and should not, be generalized. For example, a clinician/researcher may believe that an individual patient has done well in a clinical trial and thus might assume he or she has a clinical responsibility to continue the trial medication outside the research

protocol. However, in the absence of aggregate trial data, the clinician's assumption could well be false. While cumulative evidence is necessary in some types of genetic research such as those designed to study gene–disease associations and gene–environment interactions, there is a broad subset of genetic studies in which this is not the case, particularly with serious monogenic disorders for which a tight linkage assignment has been established. In such cases, the researcher may accrue knowledge from a single individual which has immediate clinical relevance not only for that individual, but also for other members of the pedigree. To argue that there is no obligation to share this data with individual subjects and/or with those responsible for their clinical follow-up, or to ensure that measures are taken to advise at-risk family members of their status on the grounds that 'these are research results and thus should not be considered as clinically relevant,' is to claim ignorance in the face of knowledge for which the researcher is morally, if not legally, responsible.

Case description

Here, we describe our experience conducting genetic research in Newfoundland, Canada (where it is likely that several serious monogenic diseases remain to be described), on one such disease: autosomal dominant arrhythmogenic right ventricular cardiomyopathy (ARVC). ARVC is a cause of sudden cardiac death (SCD) in young people (14, 15). Clinical diagnosis is difficult and is based on observational and descriptive diagnostic criteria (16). ARVC is genetically heterogeneous. It is most often inherited as an autosomal dominant disorder, and several genetic loci and cloned genes are known (17–19). One locus at 3p25 (20) contains an as-yet-unidentified gene responsible for one form of ARVC in 16 large families in Newfoundland and Labrador, including up to 1200 individuals over nine generations in a single family. Analysis of these families has determined the lethal sex-influenced natural history of the disease: 50% of males die in the absence of treatment by 40 years and 80% by 50 years, with corresponding risks for females of 5% and 20% (21). Effective primary prevention of potentially lethal arrhythmias is available with implantable cardioverter defibrillator therapy (21).

Our original consent form reflected our ignorance of the disease. That document, signed subsequent to genetic counseling, followed common practice with genetic research in that it provided assurances that were a genetic location found, further counseling would occur after molecular testing. At that point, the subject would have the option of deciding whether or not to learn his or her DNA results. Subsequent determination of a linked locus at 3p25, and the assignment of a founder DNA haplotype present in all affected subjects across families, meant that DNA testing could define disease status pre-symptomatically.

Hence, although ARVC in Newfoundland and Labrador is a lethal condition with a high recurrence risk and where effective treatment is available, DNA testing remains in the research domain. As a result, several cases have occurred where concerns have arisen regarding: (i) genetic knowledge and clinical responsibilities on the part of genetic researchers; (ii) the rights and responsibilities of research subjects with regard to their genetic information; and (iii) potential responsibilities to other family members and the general population.

Case 1

A female subject at 50% a priori pedigree risk participated in genetic linkage analysis research. The sex-influenced nature of the disease and inheritance through a female family member meant there was no immediate family experience of serious sequelae to ARVC, even though multiple SCDs in young people had occurred in the extended pedigree. Research revealed a high-risk DNA haplotype. Nevertheless, this subject refused to learn her DNA results or to receive further clinical testing. The question was raised as to whether we had a duty to warn her eight adult children, including five males aged between 20 and 40 years.

This scenario, although generated through genetic research, could occur following clinical testing, as defining affected status of the subject by any method would place the subject's offspring at 50% risk of a treatable disease causing SCD. In our opinion, clinical testing, regardless of the motivation for the testing (research or clinical), should result in disclosure to the individual. Nevertheless, this still leaves open the ethical question of duty to warn at-risk relatives. Given the lethal and treatable nature of ARVC, even those who support a conservative position with regard to sharing genetic information without patient consent, might support doing so in this situation. Indeed, emerging case law in the United States has already established that in some instances physicians may have a duty to breach the confidentiality of a patient

so as to warn family members, who are not their patients, of their risk of genetic disease (9, 22, 23). Similar provisions are available in Canadian law under the provisions of the so-called *Tarasoff* situation named for the landmark decision of the Supreme Court of California. That case recognizes that 'at some point the need to protect the public from imminent danger becomes paramount, and at that point the doctor's duty of confidentiality ends and is replaced by a duty to warn the person[s] at risk' (24). However, all of the cases cited occur within the clinical context. If the life-saving information is unavailable because genetic researchers have failed to establish working relationships with clinicians, or because researchers restrict disclosure of 'research results,' the question of contacting at-risk family members is moot.

Case 2 (a and b)

Two young males at an a priori 50% risk of inheriting ARVC participated in the research. Again, both were recruited prior to our understanding of the natural history of the disease, and thus before we appreciated the true severity of ARVC linked to 3p25 in Newfoundland and Labrador. Both subjects refused to hear their DNA haplotype results. This left the research team in the position of knowing that a serious risk of a potentially lethal but treatable condition was present; yet, due to the subjects' refusal to hear their results, the research team was unable to take steps to organize treatment with their clinical care givers.

(2a) Despite numerous overtures, the first male steadfastly refused further contact with the research team. He died of a SCD due to ARVC prior to his 30th birthday.

(2b) The second male initially refused his haplotype information, because he was training for a career for which a high-risk result would curtail his ability to continue. Furthermore, given the potential for SCD, there was a possibility that, due to the nature of the job (in transport), members of the public would be put at risk. In this case, the individual eventually agreed to receive his results, and he was treated successfully. His career plans were subsequently altered.

These, and similar cases, contributed to our consternation with regard to our duties to act upon genetic information irrespective of how the information was obtained. One result has been a modified consent document so that ARVC study participants are now required to accept that they will receive their results if and when these become available through the course of the research. If a subject does not want to learn his or her result, then the blood sample will simply not be drawn. We are considering a further amendment to the effect that if the research subject is either unwilling or otherwise unable to share clinically relevant results with at-risk family members, steps may be taken by the research/clinical team to ensure that this information is made available to those family members.

Discussion

The manner in which we frame the distinction between genetic research and clinical genetics will affect our understanding of our duties regarding the management of information accrued through genetic research. First, it is important to contrast the nature of the relationship between the researcher and the subject in genetic research with that of the clinician and patient in the clinical context. In the clinical context, patient autonomy and the assurance of confidentiality in the patient–physician relationship are often presented as key considerations in arguing against a generalized duty to warn (10, 25). However, insofar as genetic research involves families, the family must remain the primary focus of concern with regard to the management of research results.

The foregoing speaks to the importance of ensuring that genetic research is coordinated with local clinical genetics services, ideally through the mechanism of disease-based, health region coordinated, genetic registers that are sensitive to both clinical and research interests (26–29). Families are the focus of registers, and ongoing clinical care and management, follow-up of those at risk, and appropriate genetic counseling for serious diseases with high recurrence risks are their major function. When research results are obtained, they can be discussed with trained genetic professionals, and issues of potential error in research data can be addressed. Thus, in the absence of an established relationship between genetic researchers and the clinical genetics team, a research project of the nature described above could well be considered unethical. This last point has particular significance when genetic researchers are from outside the jurisdiction in which clinical services are

provided, a somewhat common scenario for genetic research conducted in Newfoundland.

Newfoundland and Labrador's population is ideal for genetic research because of its geographic and genetic isolation and large family sizes. This has been the impetus for numerous successful collaborative relationships with out-of-province genetic research teams. However, some out-of-province teams have studied Newfoundland families in the absence of local clinical genetics input. In some cases, outside researchers have abdicated any responsibility for sharing clinically significant results with research subjects or with local clinicians responsible for their follow-up, on the grounds that research results should not be applied to the clinical context. As a consequence, the province has drafted legislation to ensure that all genetic studies conducted here are subject to local ethics review. For diseases that fit the risk profile of ARVC, local research ethics board approval will occur only when satisfactory arrangements have been made through the clinical genetics service to ensure appropriate follow-up and for the communication of relevant results with subject/patients and their families. Clinical geneticists working directly with researchers in this manner may be placed under significant burden regarding potential 'duty to warn' issues that might arise. Although professional clinical guidelines in the USA, UK, and Australia permit breaking of confidentiality in 'exceptional circumstances' (30–32), the mechanism by which this would occur remains unclear. One suggestion is that health professionals be required to notify a legislated statutory body, whose remit would be to warn relatives of their risks without identifying the affected proband (5). Again, however, we note that such guidelines are aimed primarily at the clinical context and do not account for research findings.

The key consideration here is that information obtained through genetic research for serious monogenic disorders (where results from a single individual can have immediate clinical implications) differs from results generated in the course of a standard clinical trial, or in population-based, gene-association studies. The distinction, therefore, between research results and clinical application, so important in the context of clinical trials, cannot be used as the standard for genetic studies of serious diseases with high recurrence risks, particularly those for which potential ameliorative interventions exist.

Finally, it is important to mention the privacy paradox. This paradox lies in the fact of increased legislative emphasis on individual privacy protection, even as the advance of genomic medicine necessarily reveals information that is familial in nature. As noted previously, there are legal provisions and precedents in most jurisdictions that not only permit but also actually require the breach of confidentiality in the clinical context if others are in imminent danger. It is important that such provisions developed for the clinical context are applied in the research context for the kinds of cases we describe here. We are sensitive to concerns regarding genetic discrimination and recognize the need to protect individual and family privacy when appropriate. However, genetic privacy is a somewhat fickle matter, dependent to a large extent on the phenotypic expression of the particular genetic condition. Individuals with achondroplasia, for example, may have concerns about genetic discrimination, but it has nothing to do with the privacy of their genetic information. Concerns about insurability can also be misleading, as knowledge of serious genetic disease in the family has to be disclosed, regardless of individual disease status. In the case of ARVC, for example, multiple deaths in young people within the extended family will immediately affect insurability. To put it bluntly, individuals at risk of ARVC have to face the choice of dying with an insurance policy of dubious validity, because they failed to disclose relevant family history irrespective of genetic testing, or to be alive enjoying their loved ones but without insurance.

We acknowledge that ARVC in Newfoundland and Labrador is in some respects an atypical genetic disease. Hence, we do not assume that the manner in which we manage research results on this condition are generalizable to all genetic studies. However, the lessons learned from ARVC provide another perspective on the nature and extent of our obligations with regard to genetic information. This behooves genetic researchers in general and research ethics boards in particular to consider carefully the possible clinical ramifications of research data prior to embarking upon or approving a genetics research project.

We are still in the early days of the genomic era in medicine. It remains unclear whether the new wine of rapidly expanding genetic information can be contained in the old wineskins of principles, policies, and procedures for gathering, storing, and sharing medical information. Our suspicion is that one size simply will not fit all. A more nuanced understanding of the relationship between genetic research and clinical practice is essential as we move forward in this regard.

Acknowledgements

We thank Drs Anne Bassett, Terry Young, Patrick Parfrey, John Dean, Sean Connors, Andrew Latus, and Barbara Barrowman. We also thank all families with ARVC who continue to participate in research in the hope that it will further clinical progress for those who follow after.

References

1. McAbee GN, Sherman J. Physician's duty to warn third parties about the risk of genetic diseases. Pediatrics 1998: 102: 140–142.
2. Andorno R. The right not to know: an autonomy based approach. J Med Ethics 2004: 30: 435–439.
3. Clarke A, Richards M, Kerzin-Storrar L et al. Genetic professionals' reports of nondisclosure of genetic risk information within families. Eur J Hum Genet 2005: 13,5: 556–562.
4. Austad T. The right not to know – worthy of preservation any longer? An ethical perspective. Clin Genet 1996: 50: 85–88.
5. Keeling S. Duty to warn of genetic harm in breach of patient confidentiality. J Law Med 2004: 12: 235–253.
6. Leung W, Mariman E, van der Wouden J, van Amergongen H, Weijer C. Results of genetic testing: when confidentiality conflicts with a duty to warn relatives. BMJ 2000: 321: 1464–1466.
7. Knoppers BM. Genetic information and the family: are we our brother's keeper? Trends Biotechnol 2002: 20: 85–86.
8. Petrila J. Genetic risk. The new frontier for the duty to warn. Behav Sci Law 2001: 19: 405–421.
9. Clayton EW. Ethical, legal, and social implications of genomic medicine. N Engl J Med 2003: 349: 562–569.
10. Offit K, Groeger E, Turner S, Wadsworth E, Weiser M. The 'duty to warn' a patient's family members about hereditary disease risks. JAMA 2004: 292: 1469–1473.
11. Laurie G. A response to Andorno. J Med Ethics 2004: 30: 439–440.
12. Dugan RB, Wiesner GL, Juengst ET, O'Riordan M, Matthews AL, Robin NH. Duty to warn at-risk relatives for genetic disease. Genetic counselor's clinical experience. Am J Med Genet, Part C 2003: 119C: 27–34.
13. Hunter D, Caporaso N. Informed consent in epidemiologic studies involving genetic markers. Epidemiology 1997: 8: 596–599.
14. Corrado D, Thiene G, Nava A, Rossi L, Pennelli N. Sudden death in young competetive athletes: clinicopathologic correlations in 22 cases [see comments]. Am J Med 1990: 89: 588–596.
15. Shen W, Edwards W, Hammill S, Bailey K, Ballard D, Gersh B. Sudden unexpected non-traumatic death in 54 young adults: a 30 year population study. Am J Cardiol 1995: 76: 148–152.
16. McKenna WJ, Thiene G, Nava A et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial disease of the European Society of Cardiology and the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. Br Heart J 1994: 71: 215–218.
17. Ahmad F. The molecular genetics of arrhythmogenic right ventricular dysplasia-cardiomyopathy. Clin Invest Med 2003: 26: 167–178.
18. Beffagna G, Occhi G, Nava A et al. Regulatory mutations in transforming growth factor-[beta]3 gene cause arrhythmogenic right ventricular cardiomyopathy type 1. Cardiovasc Res 2005: 65: 366–373.
19. Gerull B, Heuser A, Wichter T et al. Mutations in the desmosomal protein plakophilin-2 are common in arrhythmogenic right ventricular cardiomyopathy. Nat Genet 2004: 36: 1162–1164.
20. Ahmad F, Li D, Karibe A et al. Localisation of a gene responsible for arrhythmogenic right ventricular dysplasia to chromosome 3p23. Circulation 1998: 98: 2791–2795.
21. Hodgkinson K, Parfrey P, Bassett A et al. The impact of implantable cardioverter defibrillator therapy on survival in autosomal dominant arrhythmogenic right ventricular cardiomyopathy (ARVD5). J Am Coll Cardiol 2005: 45: 400–408.
22. Pate v. Threlkel, 661 So. 2d 278 (Fla. 1995), 1995.
23. Safer v. Pack, 677 A.2d, 1188 (N.J. App.), appeal denied, 683 A.2d, 1163 (N.J 1996). Safer v. Pack, 1996.
24. Picard E, Robertson G. Legal Liability of Doctors and Hospitals in Canada. Toronto: Carswell, 1996, 181.
25. Sulmasy D. Duty to warn about hereditary disease risks. JAMA 2005: 293: 676.
26. Emery A, Brough C, Crawfurd M, Harris P, Harris R, Oakshott G. A report on genetic registers. Based on the report of the Clinical Genetics Society Working Party. J Med Genet 1978: 15: 434–442.
27. WHO. Control of Hereditary Diseases. WHO Technical Report Series, 1972, 497.
28. Dean J, Fitzpatrick D, Farndon P, Kingston H, Cusine D. Genetic registers in clinical practice: a survey of UK clinical geneticists. J Med Genet 2000: 37: 636–640.
29. Kerzin-Storrar L, Wright C, Williamson PR et al. Comparison of genetic services with and without genetic registers: access and attitudes to genetic counselling services among relatives of genetic clinic patients. J Med Genet 2002: 39: e85.
30. English V, Sommerville A. Human Genetics: Choice and Responsibility. British Medical Assoc. Oxford: Oxford University Press, 1998.
31. Committees on Clinical Genetics and Ethical Issues in Medicine. Ethical Issues in Clinical Genetics. London: Royal College of Physicians, 1991.
32. Human Genetics Society of Australasia. Privacy Implications of Genetic Counselling, 1999.