Duty to Warn and Genetic Disease

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In this clinical column, we discuss the ambiguous distinction between genetic research and clinical genetics, particularly for Mendelian diseases with high recurrence risk, high morbidity and/or mortality and the possible amelioration of such diseases by screening or treatment. We use arrhythmogenic right ventricular cardiomyopathy as an example of a lethal Mendelian disorder, which prompted the discussion contained in this column. Working with such diseases may mean that genetic researchers have some responsibility for both immediate research subjects and their extended families, as they obtain molecular genetic information. For some diseases, therefore, a willingness to accept genetic research results should be an inclusion criterion, and it may be considered unethical for research ethics boards to approve genetic studies unless measures to ensure clinical follow-up have been established. We recommend managing the tensions between genetic research and clinical practice by using disease-based genetic registers, organized within a clinical genetic service.

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Although the management of genetic information in the clinical context has been addressed in recent years (Clarke et al., 2005; Keeling, 2004; Leung, Mariman, van der Wouden, van Amergongen, & Weijer, 2000; McAbee & Sherman, 1998; Suthers, Armstrong, McCormack, & Trott, 2006), less is available on related issues in genetic research (Pullman & Hodgkinson, 2006). Standard practice is that medical research data should not be treated as though they are clinically relevant; it is assumed this standard holds for genetic research as well. We challenge this assumption. The line between genetic research and clinical practice is often ambiguous. Hence, in some cases, it may be unethical for genetic researchers to absolve themselves of clinical responsibilities on the grounds that data were obtained for research purposes. In addition, we argue that it may be unethical for ethics review boards to approve some genetic research unless advance arrangements are made for genetic counselling and clinical follow-up. In a similar vein, and contrary to standard practice, there may be cases in which it is inappropriate to enroll subjects in genetic studies unless they agree in advance to receive their DNA results and to share risk information with at-risk family members.

We use the example from Newfoundland and Labrador of arrhythmogenic right ventricular cardiomyopathy (ARVC) to illustrate our points. This genetically and clinically heterogenous disorder is a cause of sudden cardiac death (SCD), particularly in young people (Shen et al., 1995), due to tachyarrhythmias. It is extremely difficult to clinically diagnose and, as the first symptom may be SCD, early diagnosis leading to prophylactic treatment is essential. It is most often inherited as an autosomal dominant Mendelian disorder, where a single disease gene is the cause of the disorder and where the risk of inheriting the disorder from affected persons to first-degree relatives is one in two (50%).

Ambiguous distinctions

Genetic exceptionalism is the view that there is something unique about genetic information such that special consideration must be given with regard to informed consent and privacy (Green & Botkin, 2003). Some argue for special legislative provisions in this regard (Rothstein, 2005), while others maintain there is nothing unique about genetic information and that standard practices of consent and confidentiality will suffice (Holm, 1999; Sulmasy, 2005). Still others argue for at least some form of exceptionalism in particular circumstances (Launis, 2003). We will provide arguments tending towards the latter position.

We maintain that in some cases it is simply wrong to distinguish between research and clinical genetics. Although standard practice is to maintain a clear division, we reject this standard in the class of case with which we are concerned. To appreciate this line of reasoning, it is important to contrast the type of genetic research we have in mind with standard clinical trials.

The validity of clinical trial information is cumulative in nature. A perception, therefore, that a subject has benefited from participation in a clinical trial and should, therefore, receive treatment with the investigative compound in the absence of aggregate trial data, may be false. The subject may have been given the placebo. The investigative compound may have serious side effects not yet manifest in the "improved" patient. In contrast, genetic research into serious monogenic disorders may produce clinically relevant information from a single subject: relevant information for both the participant and his or her next of kin. To argue that there is no obligation to share research data with the subject, at-risk family members, or those responsible for clinical follow-up on the grounds that these are research results is to ignore information for which the researcher and the research team are morally responsible.

Amending policies and procedures: The case of arrhythmogenic right ventricular cardiomyopathy

The genetic condition that prompted these considerations is ARVC. Clinical diagnosis of ARVC is difficult, as it is based on observational and descriptive diagnostic criteria (McKenna et al., 1994) and is compounded by variable expressivity (the gene causes a different phenotype in different people) and age-related penetrance (the gene expresses at different times across the lifespan despite being present from birth). ARVC is most often inherited as an autosomal dominant trait, and there are currently several genetic loci and cloned genes (Herren, Gerber, & Duru, 2009). One genetic locus (ARVD5) at 3p25 (Ahmad et al., 1998) contains the causative gene for ARVD5: TMEM43, a cellular nuclear transmembrane protein of unknown function (Bengtsson & Otto, 2008; Merner et al., 2008). ARVD5 was found to be 100% penetrant for signs and symptoms of ARVC over the normal lifespan (Merner et al., 2008). Our epidemiological research has defined ARVD5 as a lethal, sex-influenced disorder where 50% of males die in the absence of treatment by 40 years of age, and 80% by 50 years, with corresponding risks for females of 5% and 20% (Hodgkinson et al., 2005).

Linkage to chromosome 3 was described in 1998 (Ahmad et al., 1998) and a disease-associated founder haplotype (a series of linked genetic markers surrounding the gene locus that are inherited together in affected individuals across generations) known as ARVD5 was recognized. This founder DNA haplotype at 3p25 was present in all affected subjects, so for many years prior to the discovery of the causative gene and mutation, this was used to define those most likely to have the ARVD5 gene. Now, a direct mutation analysis is used. Either method enabled presymptomatic diagnosis for those at risk. Effective primary prevention of potentially lethal arrhythmias is available with implantable cardioverter defibrillator therapy (ICD). We were able to show that the five-year mortality rate post treatment with an ICD in males was zero, which when compared with a control group from the families (who were all deceased) was significant, thus the ICD is considered the treatment of choice prophylactically in this cohort (Hodgkinson et al., 2005).

Our local research ethics policy has been influenced by our experience with ARVC. At the outset, we did not recognize the severity of this form of ARVC. Our consent form, signed after genetic counselling, followed common practice in that it provided assurances that if genetic information became available, further counselling would occur. Subjects could then choose whether or not to receive their molecular genetic results. This led to situations in which researchers knew the haplotype status of a subject, but were unable to act because the subject declined the information. This was particularly disturbing when the subject was employed in public transportation, potentially placing others at risk. Other cases have occurred when research subjects refused to inform at-risk family members of an increased risk of having the disorder: usually an increase from 25% to 50%. In response, we have amended the ARVC consent document so that subjects must now agree to receive their haplotype results as an inclusion criterion for the research. We

are still unsure as to how to deal with the subjects who are unwilling or unable to share clinically relevant information with other family members, and consideration has been given as to whether a statement should be included on the consent form to the effect that the research team will take steps to inform family members if the patient is unwilling to do so.

Wider implications

The inclusion of a statement of intent to advise at-risk family members raises a logistic quagmire. In the first place, it is necessary to determine at what point a risk is high enough to warrant a duty to warn. Even when a risk is considered high, it is both unreasonable and impractical to assume that genetic researchers, physicians, or genetic counsellors have the wherewithal to identify and contact at-risk family members. In many ways, our current situation with regard to "duty to warn" in ARVC is analogous to infectious diseases. It has, thus, been suggested (Keeling, 2004) that a central body be established to which problematic genetic cases could be referred. This body would contact at-risk family members in much the same manner as the public health department manages contact tracing for infectious disease.

There are serious issues that should be taken into account when dealing with genetic research, particularly when diseases with high recurrence risk, high morbidity and mortality, and potentially ameliorative treatment and/or screening are being investigated. We believe that it is imperative that this type of research be coordinated with local clinical genetics services through the mechanism of disease-based, health region-coordinated, genetic registers that are focused primarily on clinical interests, yet are sensitive to research (Emery et al., 1978). Research results can then be discussed with trained clinical genetic professionals, and issues of potential error in research data can be addressed (Dean, Fitzpatrick, Farndon, Kingston, & Cusine, 2000; Kerzin-Storrar et al., 2002). Thus, in the absence of an established relationship between genetic researchers and the clinical genetics team, a research project could be considered unethical.

Given the somewhat ambiguous distinction between research and clinical practice occasioned by serious genetic conditions, it may be necessary to rethink the quality standards and procedures that apply within the research context. Research laboratories that look for genes and mutations that may or may not have clinical relevance are not subject to the same standards of quality control as are clinical laboratories. Furthermore, research laboratories often train novice researchers such that much of the work is conducted by students. In light of the clinical implications associated with conditions like ARVC, however, it may be incumbent on research laboratories to ensure that such studies are closely monitored by senior scientists, and that the work is conducted according to rigorous quality standards.

Our own ARVC project is overseen by senior molecular geneticists. Because we made the decision early on to share these research results—despite the potential for genetic and sample error—our subjects were fully apprised about the limitations of the test, including the status of the laboratory doing the testing. Despite these issues, DNA haplotyping, prior to mutation testing, was still diagnostically more sensitive than any available clinical test. Our view is that the treatment benefits of a correct result are significant and outweigh the possible harm associated with providing a research high-risk result that is incorrect. To offset the alternate scenario (of providing an incorrect low-risk result), we provided regular clinical screening for all subjects until the direct TMEM43 mutation test became available.

Numerous serious conditions with high genetic recurrence risk are candidates for the kind of consideration outlined here, particularly those for which a screen or treatment is available to diminish serious morbidity or mortality. The availability of "early detection" screening for families with a cancer syndrome would argue in favour of a similar approach to research on as yet unknown familial cancer syndromes. At issue here is the degree of penetrance and the level of expressivity of Mendelian disorders (those caused by a single gene), and the decision on how to manage results made on a disease-by-disease basis.

Conclusion

Our recommendations on how to manage the nebulous distinction between genetic research and clinical practice could be challenged on practical, scientific, or ethical grounds. We have addressed some of the practical difficulties. Nevertheless, some will argue on scientific grounds that ARVD5 is a rare monogenic disorder, and most Mendelian disorders have already been identified in any case. However, many Mendelian conditions in Newfoundland and Labrador have yet to be either linked or cloned, and we expect this is true elsewhere. Some conditions being studied will present significant risk profiles that require careful attention to the clinical implications and the issue of duty to warn.

Some will challenge our conclusions on ethical grounds, believing our approach is overly paternalistic. Our response is that concerns regarding autonomy and

paternalism are but one of the many ethical matters to be considered, and must be balanced against the duty to warn. Inasmuch as genetic research involves families, our ethical responsibilities extend to all who are at risk. In the case of ARVD5, this extends to members of the public as well.

Our conclusions are not generalizable to all genetic studies due to the atypical nature of ARVD5. However, the lessons learned here provide another perspective on the evolving nature and extent of our obligations with regard to genetic information, and on an emerging duty to warn in the context of genetic research. Our observations behoove research ethics boards in general, and genetic researchers in particular to consider carefully the possible clinical ramifications of genetic data prior to approving or embarking on such studies. ♥

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References

Ahmad, F., Li, D., Karibe, A., Gonzalez, O., Tapscott, T., Hill, R., et al. (1998). Localisation of a gene responsible for arrhythmogenic right ventricular dysplasia to chromosome 3p23. *Circulation, 98*, 2791–2795.

Bengtsson, L., & Otto, H. (2008). LUMA interacts with emerin and influences its distribution at the inner nuclear membrane. Journal of *Cell Science , 121*, 536–548.

Clarke, A., Richards, M., Kerzin-Storrar, L., Halliday, J., Young, M., Simpson, S., et al. (2005). Genetic professionals' reports of nondisclosure of genetic risk information within families. *European Journal of Human Genetics, 13*, 556–562.

Dean, J., Fitzpatrick, D., Farndon, P., Kingston, H., & Cusine, D. (2000). Genetic registers in clinical practice: A survey of UK clinical geneticists. *Journal of Medical Genetics, 37*, 636–640.

Emery, A., Brough, C., Crawfurd, M., Harris, P., Harris, R., & Oakshott, G. (1978). A report on genetic registers. Based on the report of the Clinical Genetics Society Working Party. *Journal of Medical Genetics, 15*, 434–442.

Green, M., & Botkin, J. (2003). "Genetic exceptionalism" in medicine: Clarifying the differences between genetic and nongenetic tests. *Annals of Internal Medicine, 138*, 571–575.

Herren, T., Gerber, P., & Duru, F. (2009). Arrhythmogenic right ventricular cardiomyopathy/dysplasia: A not so rare "disease of the desmosome" with multiple clinical presentations. *Clinical Research in Cardiology, 98*, 141–158.

Hodgkinson, K., Parfrey, P., Bassett, A., Kupprion, C., Drenckhahn, J., Norman, M., et al. (2005). The impact of implantable cardioverter defibrillator therapy on survival in autosomal dominant arrhythmogenic right ventricular cardiomyopathy (ARVD5). *The Journal of the American College of Cardiology, 45*, 400–408.

Holm, S. (1999). There is nothing special about genetic information. In A. Thompson & R. Chadwick (Eds.), *Genetic Information: Acquisition, Access and Control*. New York: Kluwer Academic/Plenum.

Keeling, S. (2004). Duty to warn of genetic harm in breach of patient confidentiality. *Journal of Law and Medicine, 12*, 235–253.

Kerzin-Storrar, L., Wright, C., Williamson, P.R., Fryer, A., Njindou, A., Quarrell, O., et al. (2002). Comparison of genetic services with and without genetic registers: Access and attitudes to genetic counselling services among relatives of genetic clinic patients. *Journal of Medical Genetics, 39*, e85.

Launis, V. (2003). Solidarity, genetic discrimination, and insurance: A defense of weak genetic exceptionalism. *Social Theory in Practice, 29*, 87–111.

Leung, W., Mariman, E., van der Wouden, J., van Amergongen, H., & Weijer, C. (2000). Results of genetic testing: When confidentiality conflicts with a duty to warn relatives. *British Medical Journal, 321*, 1464–1466.

McAbee, G.N., & Sherman, J. (1998). Physician's duty to warn third parties about the risk of genetic diseases*. Pediatrics, 102*(1 Pt 1), 140–142.

McKenna, W.J., Thiene, G., Nava, A., Fontaliran, F., Blomstrom-Lundquist, C., Fontaine, G., et al. (1994). 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. *British Heart Journal, 71*, 215–218.

Merner, N.D., Hodgkinson, K.A., Haywood, A.F., Connors, S., French, V., Drenckhaln, J.-D., et al. (2008). Arrhythmogenic right ventricular cardiomyopathy type 5 (ARVD5) is a fully penetrant, lethal arrhythmic disorder caused by a missense mutation in the TMEM43 gene. *American Journal of Human Genetics, 82*, 809–821.

Pullman, D., & Hodgkinson, K. (2006). Genetic knowledge and moral responsibility: Ethical concerns at the interface of genetic research and clinical practice. *Clinical Genetics, 69*, 199–203.

Rothstein, M. (2005). Genetic exceptionalism and legislative pragmatism. *Hastings Center Reports, 35*, 27–33.

Shen, W., Edwards, W., Hammill, S., Bailey, K., Ballard, D., & Gersh, B. (1995). Sudden unexpected non-traumatic death in 54 young adults: A 30-year population study. *American Journal of Cardiology, 76*, 148–152.

Sulmasy, D. (2005). Duty to warn about hereditary disease risks. *Journal of the American Medical Association, 293*, 676.

Suthers, G., Armstrong, J., McCormack, J., & Trott, D. (2006). Letting the family know: Balancing ethics and effectiveness when notifying relatives about genetic testing for a particular disorder. *Journal Medical Genetics, 43*, 665–670.