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Challenges of genetic testing in adolescents with cardiac arrhythmia syndromes

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Abstract

The ability to sequence individual genomes is leading to the identification of an increasing number of genetic risk factors for serious diseases. Knowledge of these risk factors can often provide significant medical and psychological benefit, but also raises complex ethical and social issues. This paper focuses on one area of rapid progress: the identification of mutations causing long QT syndrome and other cardiac channel disorders, which can explain some previously unexplained deaths in infants (SIDS) and children and adults (SUDS) and prevent others from occurring. This genetic knowledge, discovered posthumously in many cases, has implications for clinical care for surviving family members who might carry the same mutations. The information obtained from genetic testing, in the context of personal and family history, can guide individually tailored interventions that reduce risk and save lives. At the same time, obtaining and disclosing genetic information raises difficult issues about confidentiality and decision making within families. We draw on the experience of the Montefiore-Einstein Center for Cardiogenetics, which has played a leading role in the genetic diagnosis and clinical management of cardiac channel diseases, to explore some of the challenging ethical questions arising in affected families with adolescent children. We focus on the related issues of (1) family confidentiality, privacy and disclosure and (2) adolescent decision making about genetic risk, and argue for the value of interdisciplinary dialogue with affected families in resolving these issues.

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INTRODUCTION

Few tragedies have more impact on families than the sudden unexpected death of a loved one. It can be especially devastating to lose a previously asymptomatic parent, sibling or child to a fatal cardiac arrhythmia—an event often caused by a malfunction of the cardiac ion channels (cardiac channelopathy). As a result of emerging molecular genetic research, in conjunction with forensic investigations of sudden unexpected death, it has become possible to identify an increasing number of mutations in genes involved in the functioning of cardiac channels.[12] This genetic knowledge, often discovered posthumously, has implications for clinical care for surviving family members, who can obtain preventive medical care and treatment.

Cardiac channel disorders, such as long QT syndrome (LQTS) or Brugada syndrome (BS), are often familial and are typically inherited in a dominant fashion, meaning that there is a 50% chance for any affected individual to have an affected child.[1] Guidelines for the management and risk stratification of each disorder have been established and updated; however, there are areas of diagnostic uncertainty which create difficulties in genetic counselling and clinical management.[1–3] There is wide variation in age of onset for individual disorders (2nd–4th decade for BS vs any age for LQTS), symptoms and factors that increase risk or trigger symptoms (athletic activity, drugs/medication, gender, fever, pregnancy).[1–3] Although molecular testing continues to improve, prognostic uncertainty still remains because of gaps in clinical knowledge, outdated research, insufficient statistical power, and unrepresentative data for populations with diverse ethnic backgrounds. Because patients with cardiac channel disorders are often completely asymptomatic, identifying predisposing mutations early on can lead to life-saving interventions such as drugs (antiarrhythmics or ß blockers) and behavioural changes and, in some cases, medical devices such as an implantable cardioverter defibrillator (ICD).[12]

The literature on genetic testing in minors has largely focused on newborn screening and testing children for adult-onset disorders, in particular, Huntington disease and hereditary breast and ovarian cancer syndrome.[3–6] A consensus has emerged on several guidelines for testing minors: (1) testing should not begin until the earliest age at which health benefits accrue for detectable conditions in which treatment or preventive measures exist (ie, newborn screening); (2) when there is no immediate clinical benefit to the minor, testing should be deferred to adulthood despite the minor's or parents' request for testing; (3) adolescents should be the primary decision makers about carrier testing that is relevant only for reproductive decision making; (4) testing for the benefit of another relative must have clear medical benefit and requires both parents' and minor's consent/assent.[37] Despite this consensus, recent studies indicate differences of opinion and inconsistencies in clinical practice.[38] As a diagnosis of LQTS or BS can have immediate clinical value for an adolescent, the case for disclosure and testing appear stronger. Yet decisions about testing, and about responding to test results, are often difficult because of different perceptions of 'imminent danger' and acceptability of risks. Adolescence involves a period of uncertain and uneven decision-making competence, as well as opportunities for activities that can trigger fatal arrhythmias or increase risk susceptibility. We have found that some of the greatest challenges in sharing, communicating and responding to genetic information about LQTS arise in families with adolescent children. To explore the issues facing these families, and the health professionals who counsel them, we have selected cases from our cardiogenetics centre that highlight ethical issues related to decision making, disclosure of information, and confidentiality. The Montefiore-Einstein Center for Cardiogenetics is an interdisciplinary team providing care for families who have experienced a sudden infant or other unexplained death (SIDS/SUDS) or non-fatal cardiac event. After full evaluation and extensive workup, the team meets the family to provide treatment recommendations and

elucidate risks and benefits. The effective preventive measures, based on which mutation is identified in which gene, may include lifestyle changes—such as removing alarms and other auditory triggers—medications or medical devices.[19]

Despite the availability of such interventions and the serious implications of withholding them, in several cases, adult clinic patients with adolescent children have requested that the information revealed in their genetic testing *not* be disclosed to other family members, including adolescent children. Refusal to disclose this medical information within families denies the adolescents the opportunity to become active and knowledgeable participants in their own care.[10] Moreover, it raises dilemmas for medical professionals, compelled to choose between the duty to respect the confidentiality of their patients—in this case the parents—and the imperative of preventing harm to others—the adolescents—and arguably, to respect each patient's autonomy.

Case history 1

A 15-year-old asymptomatic female adolescent is found to have a mutation that causes LQTS after an older sibling died unexpectedly, with a posthumous diagnosis of type 1 LQTS made by the medical examiner'soffice. The parents initially refused to bring their daughter to the clinic for counselling and testing; however, after several conversations with the cardiogenetics team, they disclosed the results to her and she was tested, revealing the same mutation as her deceased sibling. Individuals diagnosed with LQTS 1 are usually advised to avoid certain prescription and over-the-counter drugs that may prolong the QT interval further and restrict intense, competitive athletic activities that may lower the threshold for fatal arrhythmias. The teenage patient is unwilling to give up her participation in competitive athletic activity. Her parents are now advocating more intrusive preventive measures, including the implantation of an ICD, given the possibility of her non-compliance.

Case history 2

An adult patient who had a serious cardiac event and a genetic diagnosis of type 3 LQTS, refuses, with his wife's concurrence, to allow their 16-year-old adolescent daughter to be tested for the mutation. The parents understand that this heart condition is inherited in an autosomal dominant manner, such that their children each have a 50% risk of having the same mutation. The parents still feel that, because their daughter has been asymptomatic to this point, the health risk is not as threatening as the psychological harm that testing may cause. Given the possibility of phenotypic variability within families, there is uncertainty in prognosis, including onset and severity of symptoms. They are worried that she will take test results as bad news, which may cause more immediate harm, including depression. As parents of a minor, they have the legal right to make decisions regarding her health.

Case history 3

A 17-year-old boy with anxiety and palpitations is referred for concern that his father died suddenly in his early 30s from a fatal arrhythmia. Before visiting our clinic, the family was told by a paternal uncle that he had an ICD placed shortly after the father's death from BS.[11] We have no information on our patient's personal or family history beyond what his family has told us. The patient's paediatrician, although aware of the family history of sudden death, advised the mother not to pursue a cardiac workup until the patient turned 18, and only then to obtain a baseline ECG. During our patient's workup, her uncle was again contacted by the family, but now refuses to disclose any further medical information or release any of his medical records to relatives or health professionals. The cardiology workup for our patient reveals no abnormalities, and current genetic testing for BS via available commercial testing is negative. However, testing is only positive in about 30% of patients who actually have BS.[11] Further discussion reveals that our patient has been taking

a commonly prescribed psychiatric medication, which may be proarrhythmic and thus should be avoided by BS patients.

DISCUSSION

These vignettes present two interweaving themes: the rights and capacities of adolescents as decision makers; and the obligations of individuals to disclose their own genetic risk information to relatives. Case 1 illustrates the reluctance of some adolescents to take difficult risk-reduction measures. Cases 1 and 2 illustrate the reluctance of parents to have their adolescent children confront genetic risk. All three cases illustrate ambivalence or wariness about disclosing genetic risk information to family members: in the first two cases, to a child, and in case 3 to more distant relatives.

The disclosure and testing decisions faced by parents of adolescent children with a family history of cardiac arrhythmia differ in one important respect from the frequently studied dilemmas of parents with family histories of Huntington disease and breast cancer: potentially life-saving interventions are available when an LQTS or BS mutation is discovered. This difference appears to militate strongly in favour of testing children and adolescents for LQTS. Yet, despite the obvious benefits of testing, the parents in cases 1 and 2 were reluctant to disclose their conditions, or authorise testing for their adolescent children. In case 3, the patient's uncle refused to disclose his medical information, which would greatly facilitate the patient's genetic diagnosis. In cases 1 and 2, the parents appeared to be motivated by the desire to protect their children from the physical, psychological and social burdens of identifying a deleterious mutation; in case 3, the uncle's motives were unknown, but may have concerned the impact of disclosure on his own welfare rather than the patient's. In cases like these, clinicians are obliged to balance the needs and rights of the teens, their parents or relatives, and the clinician's own professional responsibilities and ethical convictions.[39] They present what Arribas-Ayllon has called a 'three party tension' among adult and child family members and clinicians.[12]

There are lively academic debates on confidentiality and disclosure of genetic information within families, and on the capacities and rights of adolescents to make decisions about their own health. These issues intersect in the cases we describe, where the greatest barrier to disclosure to an adolescent child is the feared impact that such disclosure will have on his behaviour and welfare. The dilemmas posed by the genetic diagnosis of LQTS suggest both the difficulty of resolving these debates, and the desirability of avoiding them through deliberation and counselling. We begin by discussing confidentiality and disclosure, and then turn to the capacities and vulnerabilities of adolescents facing a difficult genetic diagnosis.

Confidentiality, privacy and disclosure

The dual nature of genetic constitution as personal to the individual and shared by the family raises difficult issues for moral and legal analysis as well as clinical practice. As Roy Gilbar observes, 'instinctively, (people) wish to control the flow of this sensitive information. However, genetic information poses a challenge to individualistic notions of interest, for it derives from genetic material that people share with their families …'.[13]

Mainstream legal analysis has attempted to address the challenge of genetic disclosure within families under the traditional rubric of conflicting duties: confidentiality and duty to warn. The question is framed in terms of whether the doctor may or must over-ride her duty of confidentiality to the proband to inform his relatives of a serious threat to their health; the answer depends on the probability that the relatives will otherwise suffer serious harm that disclosure could prevent or mitigate.[14] One much-discussed case has held that physicians

must warn close relatives of serious, controllable genetic risks; the American Society for Human Genetics (1998) has held that they *may* do so in narrow circumstances, and at least one bioethicist (Rhodes) has argued that physicians are always bound by confidentiality.[15,16]

Others, mainly bioethicists, have argued that the clinician's duty of confidentiality to the proband is weaker, or even inapplicable, because the genetic information revealed by the proband is 'about' close family members as well. Their right to know this information does not necessarily rest entirely on the seriousness or imminence of the health risk it reveals. Some have argued that the proband must share, or offer to share, or make available any genetic information relevant to family members. Somerville and English assert that 'The luxury of informed choice should not be exclusive to the individual in the family who, by luck or judgement, is the best informed about factors affecting all'.[17] At least one bioethicist, however, suggests that the shared nature of genetic information is double-edged: because it is private not only to the proband but to his relatives, he may have a prima facie duty *not* to obtain it.[18]

In confronting the practical dilemmas of disclosure, we are not satisfied with either approach to the confidentiality of genetic information. The traditional approach is too rigid, in framing the issue of intra-family disclosure as a conflict of rights versus interests, whereas the 'common property' approach faces a host of unresolved issues concerning the boundaries of the 'genetic family,' and their competing rights to know and not know. There may be circumstances where the risk of death is so high and imminent that disclosure is required on either approach—for example, if a parent diagnosed as having LQTS1 after a near-fatal arrhythmia refuses to disclose to a child about to take part in a gruelling triathlon. But in most cases, we think that sustained communication provides a more satisfactory resolution than any theoretical approach to genetic confidentiality.

Clinicians can serve a vital role in the disclosure process. Our clinical geneticist, for example, was able to engage parents in case 1 in a dialogue about sharing the results of genetic testing with their teenager. For this process to be effective, it must be tailored to the dynamics and values of the individual family. In a review of literature about the communication of genetic risk in families, Gaff *et al* point to a variety of ways in which communication differs between and within families, including how, to whom and when to disclose one's own results.[19] There is, however, some commonality in families' attitudes: most believe there is a responsibility to share genetic information, and most desire professional assistance in delivering such information. Approaching communication of risk as a process rather than as a single event may help parents, as it did in case 1, overcome concerns about initial disclosure to their adolescent children and perhaps to other family members.

Our emphasis on process and dialogue is shared by other writers on the subject. Gilbar urges the adoption of a deliberative process 'when family tensions arise over genetic information …. (a process that) recognise that the strict rules of confidentiality should be relaxed and provide room for the ethics of the family, which is mainly based on care, commitment, intimacy, solidarity, and mutual responsibility'.[13] Arribas-Ayllon *et al* suggest that, in deciding on genetic testing for children, 'conflicts might be avoided by adopting a facilitative role,' rather than one that limits the health professional's role to 'gatekeeping access to genetic services.'[12] But it is only possible for clinicians to play a deliberative or facilitative role with families willing to talk to each other, and to their clinicians, about deeply personal concerns. Such willingness may be in short supply among geographically dispersed, emotionally distant family members, as case 3 suggests.

Genetic risk information and adolescent decision making

In our first two cases, the issues of confidentiality and 'ownership' of genetic information are complicated by the fact that the parents have an independent reason for withholding it from their child: not because the information is private, but because they are the guardians of her health and welfare, with the responsibility to withhold information that it would not be in her best interests to disclose. In case 2, the parents fear that its disclosure will be traumatic and disruptive—a widely shared concern. A similar concern was raised in a study on BRCA testing for minors, where one parent declined to test her adolescent daughter because 'it would be too traumatic,' and another declared that 'it is not necessary, in the middle of growing up. They don't need to think about it.'[7] In case 1, the parents had similar misgivings, and, although they were persuaded to share their genetic information, the adolescent refused to adopt the activity restrictions her doctor recommended. In both cases, the clinician must weigh the understandably protectionist wishes of the parents against those of the adolescent who, consistent with a typical developmental trajectory, is searching for her identity and ways to reinforce her self-esteem.

Concerns about the impact of disclosure and testing on adolescents are certainly not groundless, but they may be exaggerated. Several recent qualitative studies have looked at the reactions of adolescent and young adults (18–35 years old) to being tested for genetic conditions varying in their onset and preventability or treatability.[620–22] Those receiving positive results experienced many of the harms that parents fear—an array of negative emotions, including anxiety, anger, depression and alienation. But even a positive result for untreatable conditions—Huntington disease in particular—proved liberating for some adolescents, because it dispelled debilitating uncertainty about having the mutation, validated the pretest decision to live as if they had the mutation, and 'concentrated the mind' to plan for the future.

Our own experience in the clinic confirms these impressions. Although parents may perceive positive genetic test results as difficult for adolescent children to hear, these results provide a framework for counselling, management and decision making. Several of our families have reported that a positive molecular diagnosis provides a certainty that is useful for future family planning and provides an explanation for a previously unexplained death. Negative test results for individuals with affected relatives who have a known mutation have provided tremendous relief as well as clearance from further surveillance and testing.[1]

Parents worry about the maturity as well as the vulnerability of their adolescent children. Their reluctance to disclose their diagnosis and involve their teenage children in decision making is reinforced by doubts about adolescents' capacity to make competent decisions regarding their medical care.[23] In some respects, these doubts may be exaggerated. As Hui observes, 'several studies have shown parents' tendency to underestimate their adolescents' cognitive abilities.'[23] Though most adolescents may have the intellectual capacities to understand the clinical diagnosis, many lack the psychological maturity to accept its practical implications. A 2008 study concluded that, although cognitive abilities peak in the teenage years and impulse control becomes stronger, there is a sharp increase in the disposition to engage in high-risk behaviour.[24] Even if adolescent patients understand the risks their behaviour poses, they may be unwilling to alter it to reduce the risks associated with serious cardiac conditions. This is apparent in case 1, where the teenager is unwilling to give up competitive athletics despite the significant health risk it poses.

Yet it may be difficult to decide if the adolescent is misinformed, impulsive, or merely expressing reasonable risk preferences that the clinician and parents do not share. Individuals differ widely in their perceptions of the immediacy, magnitude and acceptability of risks. It will often be difficult for the clinician to distinguish factual error, varying risk

perception and varying tolerance for risk. It may be uncertain, for example, whether an adolescent patient is failing to grasp the probabilistic information, or instead actively choosing to live with the associated risk. If an adolescent diagnosed with LQTS expresses a reluctance to give up competitive sports because she is 'notworried aboutit,' is she revealing a failure to grasp the risk of sudden cardiac death, a strong willingness to accept that risk, or both?

Just because of this uncertainty, it is important for the clinician to engage the adolescent and his parents in sustained deliberation about risk reduction. Although dialogue and counselling cannot resolve all family conflicts or ensure compliance with difficult activity restrictions, it may help in reaching an acceptable compromise—in case 1, for example, perhaps the combination of an ICD with various safeguards or restrictions on athletic activity might yield an acceptable balance of risk reduction and continued participation.

CONCLUSION

In both areas of family conflict we have identified—intra-family disclosure of genetic information and adolescent decision making—we favour a procedural response, emphasising counselling and deliberation over any theoretical resolution of the issues. While it is important to recognise that family conflicts like those we have encountered will be increasingly common challenges in genetic medicine, it is also critical to address them in the context of particular families. We believe that the kind of interdisciplinary team we have assembled, oriented towards the integrated care of families, is well suited to meet these challenges. We are developing decision support tools to assist parents undergoing testing with discussing their results with other family members. These tools can help parents anticipate their own fears and guide their response to their children's needs and questions.

Laboratory and translational research will dramatically improve the ability to identify disease-causing mutations and offer personalised genomic medicine to families. This clinical knowledge must be matched by a better understanding of the psychological dynamics of high-risk families and the developmental complexities of their adolescent members. It also needs to be accompanied by greater sensitivity to the ethical issues posed by genetic information—as personal to the individual and common to the family. It is important to recognise that genetic medicine must be 'personalised' to the family as well as to the individual patient.

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