Ethical Dimensions of Genetics in Pediatric Neurology: A Look Into the Future

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Health care providers and families with children who participate in genetic research or who need specialized genetic services, including genetic testing, will encounter not only medical but difficult social, ethical, and legal questions surrounding pediatric genetic neurology. Children are often at the center of much of the genetic revolution and their unique needs raise special concerns about the risks and benefits associated with genetic research, particularly the issues of consent, the use of genetic databases, and gene therapy. Moreover, genetic research and testing raise important psychosocial risks. In this article we discuss some of the benefits and consequences of genetic technologies for children in relation to national and international guidelines. In particular, physicians, policy-makers, and families should be knowledgeable about the guidelines and have a good understanding of the psychosocial and ethical issues associated with genetics in pediatric neurology.

HEALTH PRACTITIONERS working with children often are confronted with difficult moral and legal decisions. Everyday neurologists, neurosurgeons, and other health providers face many ethical questions, such as whether to continue sustaining life, whether to treat critically ill newborns with profound handicaps and abnormalities, or whether to allow families to make life and death decisions for their children.[1] In addition, with the increasing demand in medical science for human research subjects, physicians in pediatric neurology are also struggling with the ethical boundaries on medical research with infants and children.[2]

With the completion of the Human Genome Project, our knowledge and understanding of the genetic components of neurogenetic diseases has advanced rapidly. Clinically these advances likely lead to better diagnoses by identifying diseases before symptoms appear, by improving the health of children with genetic conditions, or by treating neurologic cancers by gene transfer. Research plays an important role in these new emerging technologies. The genetic revolution provides hope of new treatments but also raises ethical and legal debates, especially about involving children in gene therapy research and in research on stored DNA.

Children are at the center of much of the genetic revolution. In Canada, genetic disorders constitute a leading cause of mortality and of hospitalization in children.[3-5] Approximately one third of the known 3,000 genetic diseases are neurologic or have an important neurologic component.[6] Many of these neurogenetic disorders manifest themselves early in life and constitute a leading cause of mortality and hospitalization as well as disability with important child-specific psychosocial consequences. Although many of these disorders may be of low incidence, they represent a burden on the affected individuals, their families, and society. Examples of neurologic abnormalities with a genetic component range from abnormalities in brain and spinal cord, such as epilepsy, Alzheimer's disease, Huntington's disease, or spina bifida, but also Duchenne Muscular Dystrophy. In addition, metabolic diseases, such as phenylkenonuria (PKU), or lysosomal diseases, such as Tay-Sachs and many others, have a major impact on the nervous system.

Genetic testing is one of the fastest growing areas in medical diagnostics. Genetic testing is intended to help doctors diagnose diseases and to decide on the appropriate treatment. Tests also help identify people who are likely to develop genetic disorders in adult life (presymptomatic testing); they help to learn if there is a probability they will be affected in the future (susceptibility testing); and they help identify, among those who themselves are healthy, whether they are carriers of recessive disease genes. The most heated debate about genetic testing of minors focuses on the ethical issues raised by presymptomatic and susceptibility testing for late-onset genetic disease and for testing for recessive genes (carrier status).

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Gene therapy will be a possibility in the future and many expect much from this technology, although it is still at the research stage.[7] For example, cancer cells can be modified so that they will destruct themselves or become more sensitive to treatment. In addition, gene transfer will make it possible to introduce genes in cells, which are unable to produce an essential protein. In the future somatic cell therapy will include therapy for immunologic abnormalities, hemophiliacs, Parkinson's disease, or Duchenne Muscular Dystrophy.

In a more distant future, germ-cell gene therapy may be used. It is important to draw a distinction between somatic and germ-line interventions. Somatic cell therapies modify somatic cells, which means the changes will not be passed on to the next generation. Germ-line genetics affect future generations and therefore need more public discussion.[7]

It is not possible to address the many ethical issues raised throughout this special issue of the *Seminars in Pediatric Neurology*. This issue focuses specifically on certain ethical issues raised in pediatric neurogenetics. The risks and benefits associated with genetic research are addressed, particularly the issues of informed consent, the use of genetic databases, and gene therapy. Then the psychosocial issues raised by genetic testing and gene therapies are discussed, followed by the importance of education and communication. Children and families should be informed about the benefits and consequences of genetic testing and the results of these genetic tests. In addition, communication with health professionals, ethics committees, policymakers, and public educators is important to inform them about the importance, possibilities, and consequences of genetics.

RISKS AND BENEFITS OF RESEARCH

The future of genetic research in pediatrics raises ethical concerns that are not unique. For instance, currently, research on children is governed by strict guidelines because society has an ethical obligation to protect its most vulnerable members.[2,8] Research on children involves the collection of genetic information and so raises specific issues regarding confidentiality and possible psychosocial risks. In addition, DNA abnormalities that are detected in a child will have relevance for other family members. Indeed, some family members may want to test a child to learn more about their own status. Therefore, the risk-benefit ratio for the child must include not only medical benefits and risks, but also take into account the psychosocial and familial dimensions.

Informed Consent

Informed consent is a legal necessity and an important and well-established way to ensure that research participants are aware of and agree with the risks. A review of informed consent is beyond the scope of this article. However, an extensive review of the relevant ethical and medical concerns associated with competence and capacity to consent and who should decide in a clinical paediatric neurology setting is found in the article by James Bernat in this issue. Nevertheless, we would like to further elaborate on the legal issue of involving minors in genetic research. Consent in this area is complicated by the uncertain legal definitions in the context of pediatrics.

Rarely is the issue of the participation of children specifically addressed in law.[8a] Although the age of access to medical treatment is sometimes enshrined in law or individually determined, depending on the maturity of the minor, statutory or case law determination of the age of "capacity" to participate in research is conspicuously absent. Seen negatively, this absence could be determined as excluding them from research in the absence of explicit parental authorization. Or, arguments could be made in favor of extending the statutory age provision or mature minor role applied in medical treatment, to research involving minors with the added proviso of (at a minimum) parental notification.

Assessing Risk in Pediatric Genetic Research

Research entails some degree of uncertainty about the degree of risks and benefits. There is strong consensus that research on children can only be carried out when there is minimal risk to the participant's health or when it is not possible to obtain the same scientific results with other research subjects.[9-12] In addition, the participant should either directly benefit from the treatment or other children of the same age or condition should eventually benefit.[11,13]

Some research guidelines maintain that there is an obligation to be even more risk adverse and to show that the research has the potential to benefit the particular child.[14] However, blanket exclusion

of children from genetic research because of the unknown risks and benefits could be detrimental both to affected children and to those potentially at risk. Increasingly, it is recognized that research involving the child can be important for the benefit of other children. Thus, even research not intended to directly benefit the child is not necessarily either unethical or illegal.[12,15] For example, the Canadian Tri-Council Policy statement encourages researchers not to exclude prospective and actual subjects on the basis of age and recommends considering the participation of children.[15]

Yet, for the area of genetic research, the Council in article 83 maintains that:

> As in other areas of research ethics, genetic research involving children involves special ethical obligations and protection. Children may be at particular risk for stigmatization both within and beyond the family because of knowledge gained through genetic studies. Therefore, genetic research involving children should not be done unless an effective intervention is available and the information to be gained outweighs the risk of harm. It may be appropriate, for example, to offer testing to children in a family for an early onset condition such as polyposis coli, for which the knowledge affects treatment options, but inappropriate to test children for an adult onset condition such as Huntington Disease for which no effective prevention yet exists.[15]

This latter approach has been adopted internationally. Even in the absence of direct benefit, the Council of Europe (1997) in article 17^2 of the Convention does not prohibit research on children with an unknown benefit as long as the research is "capable of conferring benefit . . . to other persons in the same age category or afflicted with the same disease or disorder or having the same condition . . . and entails only minimal risk or minimal burden."[11]

Decisions to involve children in research with a view to developing a new genetic test may be problematic if the research is carried out to develop new tests for carrier status or for predictive purposes when there is no therapeutic potential, treatment or preventive strategy. Many policy groups and professionals consider testing children for the benefit of the family, for carrier status, for late onset-disorders, for susceptibility or for predictive purposes as inappropriate and unacceptable.[13,16,17]

Use of Genetic Data Bases for Research

The availability of DNA in genetic databases is useful to help understand gene function, the prevalence of genes in populations, and for medical research. The use and storage of DNA (DNA banking) is an important issue because DNA is a very stable molecule and can be stored easily for a long time. Therefore, newborn blood spots and DNA, stored in scientific laboratories, can be used over time and for purposes that were not intentionally agreed on. The range and diversity of issues surrounding DNA banking is vast and includes the following: consent to use it for other purposes than originally intended (secondary uses), re-contact, confidentiality, and destruction, to name but a few.[18] For example, if the information in the databank is to be used for research purposes, it is generally unacceptable to use identifiable information without the person's consent. To avoid breach of confidentiality, all genetic information could be stripped of identifiers and rendered anonymous. Moreover, information should be given to the individual about the use of anonymized samples in the future. Protocols could also foresee the coding of the sample, although this raises issues about re-contacting the family and the possibility of access by insurers, employers, or other third parties.[18]

Gene Therapy

The therapeutic potential of gene manipulation raises a number of profound social, ethical, and legal issues. Perhaps the most poignant example of gene therapy is the case of Jesse Gelsinger. His death at the age of 18 years following a gene therapy trial in 1999 stimulated a debate on the evaluation process and monitoring of clinical trials.[19]

Gene therapy is a novel and innovative treatment, which may have an important, positive impact on medicine in this century. Because children may benefit extensively from this therapy, trials are likely to involve very young children. There are many socioethical concerns inherent in gene therapy including difficulties weighing risks and benefits; and the need for monitoring and follow-up for the lifetime of the person. The medical consequences of gene replacement therapy are not fully evaluated and may result in unexpected side effects. Potential harms to individuals who are subjects of such research are poorly understood and hence could be over or under estimated.[20] This has recently been shown with gene replacement therapy for Parkinson's disease, where about 30% of

the patients who successfully received the gene encoding tyrosine hydroxylase to boost dopamine levels suffered severe side effects because of a too high production of dopamine.[21]

The Council of Europe and others have adopted positions concerning gene replacement therapy, which recognize that the therapy must be conducted for medical reasons and not for cosmetic, behavioral, or enhancement reasons.[11,22,23] The Council of Europe clearly states in article 13 of its Convention that "an intervention seeking to modify the human genome must only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descents."[11] In some circumstances it is important to recognize that some parents may be overeager to seek a "permanent" treatment for their child, for whatever reason, and so may volunteer their children for medical research.[24] Consequently, special precautions must be taken to protect the children to ensure that the decision to enroll a child in a gene replacement trial is only taken in the best interest of the child.[25]

PSYCHOSOCIAL RISKS IN GENETIC TESTING AND SCREENING

In clinical genetics and research, risk needs to be defined in broader terms than merely physical harm. Unlike the physical pain associated with a blood test, the risks associated with genetic information do not stem from the procedure itself and are more likely to be social and psychological for both the child and for the family.[17,26] As well as the minor physical risks attached to the blood test, psychosocial risks are important, especially in children, because of the possible long-lasting psychosocial effects and possible interference with further development of the child.[27]

For example, genetic testing of children can pose far-reaching psychosocial risks—damage to a child's self-esteem, heightened levels of anxiety, loss of future autonomy, discrimination in education, barriers to employment and insurance, and difficulties in forging future relationships.[28-30] Indeed, simply undergoing a genetic test, in and of itself, can trigger these consequences, regardless of the results of the test. These risks are to be taken seriously because, in contrast to adults, not all children have the ability or opportunity to decide for themselves whether they want to be tested. Moreover because of their dependence, genetic information is communicated to the parents. This raises a host of questions about the timing, value, and appropriateness of explaining this to the children. When should parents reveal results to their children? Should parents reveal these results at all, if the disease is untreatable or late-onset, or if the child is a carrier? What if the test is positive, but has a poor predictability?

It is worth noting that the psychosocial effects of screening affect parents as well as children. Screening can trigger anxiety in parents, affect family relations, and lead parents to treat children differently after a positive result. For example, a study in Sweden showed that parents with children with α_1-antitrypsin deficiency responded to this situation by increased smoking,[31] which is not only damaging for themselves but also for the children. Other studies mentioned by Michie[32] revealed that, after a child tests positive in presymptomatic screening, some parents tend to treat their still-healthy child as if they already had the disease. Thus, given the current level of uncertainties and in the absence of clear medical benefits, most policy and professionals groups agree that testing of children is inappropriate and that the best interests of the child should prevail.[33]

Many of the psychosocial issues concerning genetic research in children overlap with those encountered in the clinical setting. Genetic testing or screening is usually recommended if there is an effective intervention. For example, in the case of neurofibromatosis, a disorder where benign tumors affect the nervous system and which can lead to deafness, blindness, and life in a wheelchair, genetic testing facilitates better monitoring, and early surgical treatment particularly during adolescence.[34] Unless there are clear benefits, genetic testing of children should be avoided.

In addition, the potential use of genetic information for social purposes by third parties including schools, employers, and insurance companies is a source of concern.[28] Genetic information could be misused to discriminate and stigmatize people. For instance, there is a growing concern about the potential use of genetic information by insurance companies and other third parties, including schools, governmental agencies, adoption agencies, immigration departments, and future employers.[35] Furthermore, many countries are wrestling with social attitudes to handicaps and social perceptions of "abnormality." In this respect, the stig-

matisation of people with neurologic disorders is already a social problem, and this may further contribute to such prejudices and beliefs.

Clinicians as well as researchers have a duty to advise their patients or research subjects of the possible psychosocial risks. These burdens need to be taken into consideration in the risk/benefit analysis, especially because in contrast to adults, not all children have the ability and opportunity to decide for themselves when or whether they want to participate in research or predictive genetic testing. Despite the concern about the impact of genetic testing, there has been little research on critical issues affecting children, such as how parents assess risks and benefits of presymptomatic screening; and how children react to positive test results. Consequently, before expanding the use of genetic tests and development in genetic research, there needs to be a better understanding of the psychosocial risks and benefits. How does one assess minimal risk, particularly psychosocial outcomes? Do we focus on procedures or on outcomes? How does one assess harm from the perspective of the child while taking account of their varying competence? Therefore, a child or family considering predictive genetic testing should be given information about the advantages and disadvantages, the uncertainties, and assurances that the information will be confidential.

COMMUNICATION AND EDUCATION

To give an informed consent, whether for genetic research, for genetic testing or screening purposes, or for gene therapy, the child or the family needs to understand the nature and purpose of the procedure as well as understand the risks and benefits. Therefore, the importance of communicating these issues is primordial, and the unique needs of children and families must be kept in mind. In addition, to further effectuate this communication, genetic education about social-ethical and legal issues should feature prominently in research ethics committees, among health professionals, and in the general public.

Communication With Children

Our discussions about what is right for children usually reflects our adult stereotypes of what children feel and think. We expect children to accept our adult views and generally we provide little opportunity to express their views. We often forget that they should be able to direct their own lives to the best of their abilities.[36]

In the past, health professionals have downplayed children's capacity for decision-making, and responded in a paternalistic way. Indeed, evidence suggests that children are given little voice in medical consultations and are not consulted as partners in their care.[37,38] Nevertheless, there is a growing recognition that children are capable of complex health decisions, earlier than previously believed.[39] Increasingly, several policy statements recognize that maturity and competence are fluid concepts; that children should participate in important decisions about their lives as early as possible; and if they are too young to consent, the child's assent should be sought.[10,11,13,15] These positions are consistent with The United Nations Convention on the Rights of the Child. Article 12 states that "Parties shall assure to the child who is capable of forming his or her own views the right to express those views freely in all matters affecting the child, the views of the child being given due weight in accordance with the age and maturity of the child."[40]

According to the World Health Organization, to obtain a child's assent, the potential harms and benefits will need to be explained in a simple manner.[13] However, studies have shown that although physicians' understand the importance of valid consent, the practice of obtaining consent rarely occurs according to recommended standards (see the article by Bernat elsewhere in this issue).

Thus, a child capable of expressing his or her assent or dissent regarding a medical intervention should be consulted. His or her opinion should carry equal weight in the decision-making process. Even if a child lacks the capacity to either assent or consent, it is nevertheless good practice to involve the child as much as possible in the decision-making.[41] This means that medical procedures must be communicated to the individual in clear, age-appropriate language and in partnership with them. Appropriate time should be provided for discussion and ongoing questions.

Communication With Families

Communicating with children is triadic because the relationship also involves the family and the health professional. Families are the center of children's lives and have the greatest interest and concern for the child. The family environment is

highly important for children to develop caring relationships, to develop their own competencies, and to learn how to communicate.[42] Parents and other adults play a critical role in the development of children, whether in traditional or extended families, and they should play an important role in the communication.

Traditionally, the information given by health professionals to family members has been paternalistic. However, there is now a growing realization that information is a two-way exchange, with families providing information about the child and the professionals responding with their knowledge and experiences. This is most relevant when dealing with genetic information because this information has relevance for other members of the family. Given that the family is key in the child's life, a family-centered model involving the family is justifiable and desirable.[43] Such a family-centered care approach has been adapted by the Council of Regional Networks for Genetics Services (1996), which recommends that "professionals should serve patients and their families with equity and with respect for each person's feelings, beliefs, ethno-cultural traditions, and social circumstances."[44]

Access to counseling and informed advice is particularly important in the case of parents, children, and youths facing genetic screening. Not only are the stakes high for those who will have to cope with the results of such tests for the rest of their lives, but explaining the procedure and its implications to children is a challenging task that requires solid training.

Ethics Committees

Research ethics committees provide an important layer of protection to safeguard children in research studies and institutional committees provide an important vehicle for bridging and improving communication, and for conflict resolution. Although family and community involvement is desirable, the mechanisms and priorities are not yet clear (see the article by Shevell elsewhere in this issue).

Although research review committees seem adequate for much of the research currently being done, this may not be so for the follow-up. Whenever a project is approved, efforts must be made to monitor the implementation and the outcome of the study. Hence, there are calls for vigilance on the part of research ethics committees to play an important role in protecting the subjects and address possible psychosocial controversies.[12] Ethics committees should continuously monitor the research protocols to guarantee a favorable risk-benefit ratio.[45]

Education: Professionals in Ethics and Genetics

There is general agreement that professional educational systems, such as universities and professional bodies, have failed to prepare professionals to respond adequately to ethical issues generated by the medical technologies and the genetic advances. For instance, most clinicians generally receive little formal training in ethics and on the social psychological and legal implications of genetic technology.[46,47] Moreover, they are often ill equipped to deal with decision-making in end of life situations, in the determination of medical futility, and in the management of critically ill newborns and of children in persistent vegetative states.[48]

Health professionals often lack a through understanding of the social, ethical, and legal impact of, for example, genetic screening and predictive testing on children and their families.[49] In particular, the National Human Genome Research Institute (NHGRI) program for ethical, legal, and social implications (ELSI) has expressed concern about the poor understanding of human genetics by health care providers and other allied health professionals.[50]

Given the far-reaching implications of genetic information, access to pre- and post-testing and screening counseling is essential. There is a shortage of such counseling services and trained counselors.[51] Some say such services will be nearly impossible to deliver if the demand for genetic testing increases, as expected. Moreover it has been reported that physicians and other health professionals have difficulty understanding the effects and consequences of genomic science and frequently fail to recognize patients who may benefit from genetics services. In addition, they often lack the skills for nondirective counseling.[33]

This concern is all the more pressing because there will be too few genetic counselors to meet the increasing demands for genetic services. It is anticipated that the responsibility will be placed on the shoulders of primary care physicians. Although physicians would have a better personal bond with

their patients, surveys also show that physicians are inadequately trained in genetics and the application of new technologies and have not been exposed sufficiently to the new issues of genetic medicine.[47]

Therefore, to minimize many of the socio-ethical problems that arise out of the Human Genome Project, three measures are required according to McKusick: "Education, Education and Education."[52] In response to these needs, the American Medical Association Accreditation Council for Graduate Medical Education requires education in ethics for all licensed residents (http://acgme.org/). In addition, many medical schools have begun to include human genetics in their curriculum.[53] It is unknown whether the social-ethical consequences are generally part of such a curriculum. However, there remains a great need to update the physicians already practicing who have not had sufficient medical training in medical genetics.

Informed consent of the patient is a legal necessity and an important and well-established way to ensure that research is carried out ethically. Health professionals have a duty to keep informed of the legal consequences of their practice and should be knowledgeable about the laws governing patients and medical research, especially with children, and their actions to initiate or terminate medical treatment. Legal constraints are influenced by state or provincial laws, case law, and medical malpractice law.[41,54]

Education: Public

Not only physicians, but also policy-makers and the public must come to grips with of the complex ethical, legal, and social questions resulting from the new genetic technology. Policy-making on human genetics should be grounded in the most informed opinion available about research on children and young people, the current developments in gene therapy testing and screening, and other genetic applications such as gene transfer. Guidelines and policy documents on legal, social, and ethical aspects of human genetics are being continuously developed worldwide.[55] The HUMGEN website http://www.humgen.umontreal.ca/, developed at the Centre de Recherche en Droit Public at the University of Montreal provides easy access to policies on human genetics from all over the world and gives valuable information about the political landscape. It can serve to guide and assist in the adoption of successful approaches and promote international harmonization. Many authors recommend determining the balance of potential benefits and risks of a genetically based procedure, whether genetic testing or gene transfer, before making a decision. Moreover, research currently indicates that meaningful public participation in genetic policy-making is rare and careful consideration to promote public participation in medical policy-making deserves attention.[56]

CONCLUSION

As more information accumulates about genetics and its applications, families with children who participate in genetic research or testing in the field of pediatric neurology will encounter not only medical but also social, ethical, and legal issues. Likewise, health professionals, who provide genetic services for the children and their families, and policy-makers, who are asked to help to regulate this rapidly growing field, will face similar ethical concerns.

Children have specific problems and unique needs in this field. For instance, genetic testing of children raises questions about issues such as competence, consent, confidentiality, and the psychosocial impact of the tests. Genetic information can have negative effects on children, and this potential effect is difficult to predict because of the evolving capacity of children. Given the possible harmful effects on a child's opportunities and freedom of choice, most guidelines maintain that the use of genetic tests of children is inappropriate for untreatable disorders; for late-onset disorders; for carrier status testing; and, finally, for nonmedical purposes. We agree that such testing should be delayed until the child can make the decision on his or her own.

Yet, it is important not to preclude children from potentially beneficial genetic research, such as gene therapy, although involving children in research requires measures that will protect them. Most guidelines concerning research and children support the child's right to self-determination. When the child does not have the legal capacity to consent, many guidelines recommend involving children in the decision-making process by seeking their assent. In that respect, research ethics committees should not only consider issues of consent and assent but also the potential benefits and risks for the participants of

research studies, thereby providing an additional layer of protection for children.

Genetics will have a major impact on all areas of medicine. Physicians and other health care providers will need sufficient understanding of the socio-ethical and legal issues. The likelihood that patients receive proper and updated information and support from their physician is not always enough. At the moment health professionals lack adequate training and have a poor understanding of the psychosocial and ethical issues associated with genetics. It is essential to address these concerns. Attention needs to be paid to communication with children and families. The same holds true for policy-makers and the public at large. It is therefore of the utmost importance to educate the public and policy-makers alike. In the absence of such an approach, there can be no rational discussion of all the benefits and consequences of these new and exciting technologies.

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