

# GROWING UP AS A RESEARCH SUBJECT: ETHICAL AND LEGAL ISSUES IN BIRTH COHORT STUDIES INVOLVING GENETIC RESEARCH

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## Introduction

Many population genetic research projects seek to recruit women during pregnancy or infants at birth for longitudinal birth cohort studies that investigate how early environmental conditions interact with a child's genome to increase disease susceptibility or confer protective effects.<sup>1</sup> Researchers worldwide are sleuthing for genetic factors related to major child health problems such as obesity, diabetes, behavioural disorders, allergies and asthma. These research initiatives depend on the availability of biological samples collected periodically from children, their mothers and sometimes other family members – often including samples of blood, placenta, hair, nails and urine – and collection of information about lifestyle, environmental exposures and health. One commentator observes:

Increasingly, research involving children uses longitudinal designs to identify the developmental trajectories of environmental health problems and the single or joint health effects of heredity and prenatal and postnatal exposure to environmental agents. By its nature, such research often involves asymptomatic children who will or will

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1 See Table 1 (p. 268) for a summary of birth cohort studies that involve genetic research. See e.g. Francis Collins, "The Case for a US Prospective Cohort Study of Genes and Environment" (2004) 429 *Nature* 475 (for analysis of the arguments favouring investment in prospective cohort studies).

not be affected by environmental agents under investigation or who will develop a disorder previously not known to be associated with an environmental agent.<sup>2</sup>

Birth cohort studies are notoriously challenging and expensive to design and implement. Indeed, “such studies involve a long-term contact with the participating families where the children, in some cases, will be born and grow up during the project.”<sup>3</sup> This feature contributes to the immense scientific value of cohort studies, but also is the source of many legal and ethical concerns.

Infants and young children are incapable of giving consent to participate in health research, so parents or guardians must give their permission for a child to take part. But legal and ethical rules limit parental rights to permit a child to participate in research, particularly research that is of no direct benefit to the child. How do these limits apply to parental permission for an infant to become part of a birth cohort that will follow the child’s health and development over many years?

As children mature, they develop capacity to make their own choices about whether they wish to continue participating in research. Empirical studies of minors’ capacity to consent suggest that psychosocial maturity to understand the nature of research activities and the rights of research subjects develops by age seven to 10, and by age 14 to 16 an adolescent’s capacity is generally the same as an adult’s.<sup>4</sup> In a cohort study, where a child grows up as a research subject, when – if at all – does a child have a right to express his or her own, independent choice about continuing to participate?

Long-term studies involving genetic research also raise special informational privacy risks. Vast amounts of personal information are collected and analysed over the course of a cohort study and genetic research may reveal previously unknown – and possibly unwelcome – information about partici-

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2 Celia B. Fisher, “Privacy and Ethics in Pediatric Environmental Health Research – Part II: Protecting Families and Communities” (2006) 114:10 *Environmental Health Perspectives* 1622.

3 Ulrica Gustafsson Stolt, Per-Erik Liss & Johnny Ludvigsson, “Nurses’ views of longitudinal genetic screening of and research on children” (2005) 14:2 *British Journal of Nursing* 71.

4 Jean-Marie Bruzzese & Celia B. Fisher, “Assessing and Enhancing the Research Consent Capacity of Children and Youth” (2003) 7:1 *Applied Developmental Science* 13.

pants and their biological relatives. Researchers must implement robust confidentiality and security measures to safeguard participants' information and must also develop policies about returning research results to participants. Finally, researchers must be aware of potential obligations to report information acquired in the course of research to third parties, such as concern that a child is at risk of abuse or neglect.

This article begins with an overview of the general rights of research participants and the special context of birth cohort studies involving genetic research, then analyses in detail legal and ethical issues related to consent for children to participate in research, risks and perceptions of risk, factors that motivate research participation, conflicts between children and parents over participation in research, rights to withdraw from research and duties to report information acquired during the course of the research, including results of research tests. Applicable ethical and legal principles in Canada, the United States, Australia and the United Kingdom are discussed to provide a comparative context for examining these issues. Two tables accompany this article: Table 1 (p. 268) summarizes pediatric population genetic initiatives in progress or development in North America, England and Scandinavia, and Table 2 (p. 270) extracts key provisions in select ethics guidelines regarding minors' participation in research in Canada, the United States, the United Kingdom and Australia.

## General Rights of Research Participants

Participants in research are entitled to various rights and protections based on fundamental ethical principles of respect for autonomy and dignity of persons. These include rights to: give voluntary, informed consent; receive comprehensive and understandable information about the nature, goals, risks and benefits of the research; protection of personal information, especially identifiable information; and withdraw from participation at any time without repercussion. These research rights have been formalized in numerous national and international research ethics guidelines.<sup>5</sup> Many ethical and

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5 Royal College of Pediatrics and Child Health, Ethics Advisory Committee, "Guidelines for the Ethical Conduct of Medical Research Involving Children" (2000) 82:2 Archives of Disease in Childhood 177 [Royal College Guidelines]; Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (Geneva: Council for International Organizations of Medical Sciences, 2002); World

legal concerns are heightened in research studies with pediatric populations. As research participants, children “are more vulnerable than adults because of cognitive and emotional development, level of autonomy, and dependence on family influence.”<sup>6</sup> Indeed, “[c]hildren are not small adults; they have an additional, unique set of concerns”<sup>7</sup> in regard to research participation.

Only persons with “capacity” can give legally valid consent to participate in research<sup>8</sup> and, as a general ethical principle, it is preferable to con-

Medical Association, *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects* (Edinburgh: 52<sup>nd</sup> WMA General Assembly, 2000) [Declaration of Helsinki]; Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada & Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (Ottawa: Interagency Secretariat on Research Ethics, 1998, with 2000, 2002 and 2005 amendments), online: Government of Canada <[http://pre.ethics.gc.ca/english/pdf/TCPS%20October%202005\\_E.pdf](http://pre.ethics.gc.ca/english/pdf/TCPS%20October%202005_E.pdf)> [Tri-Council Policy Statement].

6 Gail Geller *et al.*, “Informed Consent for Enrolling Minors in Genetic Susceptibility Research: A Qualitative Study of At-risk Children’s and Parents’ Views About Children’s Role in Decision-making” (2003) 32 *Journal of Adolescent Health* 260.

7 Royal College Guidelines, *supra* note 5.

8 Article 1 of the Nuremberg Code (1947) emphasizes the vital importance of obtaining voluntary consent from persons who have capacity to understand the nature and consequences of participating in research:

The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. (Available online: <http://ohsr.od.nih.gov/guidelines/nuremberg.html>)

See e.g. *Weiss v. Solomon*, [1989] A.Q. 312, 48 C.C.L.T. 280 (Sup. Ct.). See also

duct research only with those who are capable of giving their own informed consent. Capacity refers to the cognitive ability to understand the nature and consequences of research, including any anticipated risks and benefits. Adults are presumed to have capacity to consent, unless there is reason to believe otherwise (for instance, in geriatric populations, some individuals may have mental impairments that diminish their capacity to consent to participate in research). Children, in contrast, are presumed to be incapable of giving consent to participate in research.

In light of their legally incompetent state, the participation of children in research has been controversial. The 1947 Nuremberg Code completely excluded children and incompetent adults from biomedical research and the 1964 World Medical Association Declaration of Helsinki only permitted inclusion of children if research had the possibility of diagnostic or therapeutic benefit. This requirement was removed in a 2000 revision that permits inclusion of children provided the research is of general benefit in promoting health and advancing knowledge of disease in pediatric populations.<sup>9</sup>

Prior policies of excluding children from research created ethical problems as it hindered advancement of knowledge about pediatric health issues and forced clinicians to rely on research with adults in developing treatment protocols for children. Denying children the benefits of research into their unique health circumstances renders them “therapeutic orphans”<sup>10</sup> but, as Kodish observes, “we appear to have entered a new era in attitude and policy, and are making real progress toward rectifying this historical aversion to pediatric research.”<sup>11</sup> Contemporary consensus is “that research that is of no intended benefit to the child subject is not necessarily unethical or illegal”<sup>12</sup> and prevailing ethical norms accept parental (or other authorized decision-maker’s) permission for children’s participation in research provided other research protections exist.

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*Halushka v. University of Saskatchewan* (1965) 53 D.L.R. (2d) 436 (Sask. C.A.) (Canadian law also emphasizes the need for researchers to obtain voluntary, fully informed consent from research subjects).

9 For discussion, see Bartha Maria Knoppers *et al.*, “Children and incompetent adults in genetic research: consent and safeguards” (2002) 3 *Nature Reviews Genetics* 221.

10 Eric Kodish, “Informed Consent for Pediatric Research: Is It Really Possible?” (2003) *Journal of Pediatrics* 89.

11 *Ibid.* at 90.

12 Royal College Guidelines, *supra* note 5.

As regards research with incompetent persons, ethics guidelines have historically distinguished between therapeutic and non-therapeutic research. However, this distinction is increasingly “regarded by many as unhelpful and potentially misleading”<sup>13</sup> as it obscures the facts that research intended primarily to benefit a child may nonetheless involve non-therapeutic elements (e.g. blood draws) and that research “which cannot directly benefit the child is not necessarily unethical if the findings might benefit future generations of children.”<sup>14</sup> Some ethics documents, including the Declaration of Helsinki and the U.K. Medical Research Council Ethics Guide for research with children no longer make this distinction.

However, all ethics guidelines address the concept of risk; indeed, assessing the anticipated degree of risk and benefit associated with a research protocol is a key function of ethical review bodies. Also ethics documents uniformly identify a need to protect incompetent participants, including children, from unacceptable research risks. Ethics guidelines typically define risk along a continuum ranging from minimal to high, though specific definitions vary among jurisdictions (see Table 2, p. 270). In general, minimal risks in research are those that are no more serious or likely to occur than risks the person encounters in daily life.<sup>15</sup> Minimal risk activities include noninvasive collection of biological samples (e.g. saliva or urine) while blood draws are categorized by some ethics rules as low, rather than minimal risk, as they may involve temporary discomfort.<sup>16</sup>

In research involving children, the degree of risk and benefit is critical in determining if their participation, based on parental consent, is ethically acceptable. Indeed, it is debatable whether a parent can permit their child to participate in research involving anything more than minimal or low risk where the research is of no direct benefit to the child.<sup>17</sup> This raises the prob-

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13 Medical Research Council, *MRC Ethics Guide: Medical research involving children*, online: Medical Research Council <<http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002430>> at 14 [MRC Ethics Guide].

14 *Ibid.* at 14.

15 See Tri-Council Policy Statement, *supra* note 5, Article C.1. See also United States Federal Code, *Protection of Human Subjects*, 45 C.F.R. §46.102 (2005) [C.F.R.].

16 See e.g. MRC Ethics Guide, *supra* note 13 (the relevant provisions are summarized in Table 2, p. 270).

17 As discussed below, Canada’s Tri-Council Policy Statement seems to preclude parental permission for anything above minimal risk research.

lem of identifying the type and magnitude of risk to which a child is exposed as a participant in a birth cohort study involving genetic research.

## **The Special Context of Birth Cohort Studies Involving Genetic Research: What are the Risks?**

Genetic research studies, especially long-term biobanking initiatives, create a unique research context as they involve collection, storage and use of biological samples over many years, can reveal new medical information about participants and their biological relatives, and can raise unique dilemmas related to obtaining consent, protecting individual privacy and communicating findings to participants. The types of potential harms to which participants may be exposed in longitudinal population genetic studies are generally different from harms that arise in clinical research of drugs, medical devices or other therapeutics. The latter category typically involves invasive intervention into a participant's body with risks of physical harm. In contrast, population genetic research primarily involves noninvasive collection of biological samples and compilation of personal information where concerns about informational privacy overshadow physical risks. However, some research projects within a broad population genetic initiative may involve more invasive testing procedures. For example, a sub-population of the entire cohort may be asked to undergo tests to measure lung, cardiac or other functions that involve additional discomfort and risks. In some cases, these tests require sedation of a child, use of uncomfortable equipment and additional blood or fluid draws.

At minimum, participation in a cohort study involving genetic research will require the taking of biological samples from a child. This may involve collection of bodily materials that would otherwise be waste (e.g. urine, nail clippings) or deliberate taking of blood or other fluids. A blood draw may involve minor bruising and temporary emotional distress for a child who is frightened of needles. In its guidelines on ethical research with children, the British Royal College of Paediatrics and Child Health notes: "Many children fear needles, but with careful explanation of the reason for venepuncture and an understanding of the effectiveness of local anaesthetic cream, they often show altruism and allow a blood sample to be taken."<sup>18</sup> However,

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18 Royal College Guidelines, *supra* note 5.

blood should not be drawn “if a child indicates either significant unwillingness before the start or significant stress during the procedure.”<sup>19</sup>

Some studies involve more invasive tests than blood draws and these raise questions about the ethics of procedures such as sedating infants for research purposes. One author notes that “[s]ome ethics committees are prepared to consider sedation of healthy infants for nontherapeutic research, but this is becoming more exceptional, and there is a move to develop tests which can be performed during natural sleep without the need for sedation.”<sup>20</sup> However, in her view, “the use of sedation itself is neither ‘ethical’ nor ‘unethical’ and it should be considered in the context of the whole proposed study and as part of the benefit:risk equation.”<sup>21</sup>

In addition to physical tests, longitudinal cohort studies compile significant amounts of lifestyle and health information about children and their families from various sources, including questionnaires and interviews of individual research participants and links with administrative databases and registries of health and other personal information. In a long-term cohort study, this data collection compiles “a substantial amount of information regarding diverse areas such as working environment, exposures, employment, drinking habits, nutrition, psychosocial aspects regarding social support, parental stress, serious life events, etc.”<sup>22</sup>

To date, little research has explored how parents and children perceive risks of participating in longitudinal genetic research studies.<sup>23</sup> The following quotations from a father and a 16-year-old suggest that parents may view genetic research as less risky than other forms of research:

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19 *Ibid.* at 179.

20 Caroline S. Beardsmore, “Ethical Aspects of Respiratory Research in Infancy and Early Childhood” (1998) 26:1 *Pediatric Pulmonology* 64.

21 *Ibid.* at 66.

22 *Supra* note 3 at 75.

23 Other studies have examined views of the public – typically surveys of adult members of the general public or adults involved in health care or research – regarding genetic research and issues of privacy and consent. For review of such public opinion research, see e.g. Mary R. Anderlik & Mark A. Rothstein, “Privacy and Confidentiality of Genetic Information: What Rules for the New Science?” (2001) 2 *Annual Review of Genomics and Human Genetics* 401. See also Timothy Caulfield, “Biobanks and Blanket Consent: The Proper Place of the Public Good and Public Perception Rationales” (2007) 18:2 *King’s College L.J.* 209.



If you're just talking about spitting in a cup, he [the child] could make that decision ... but when you're talking about putting a drug into his body, that's a different story... (Father)

If it's just spit, I think I could decide that. I mean obviously I'd want my parents' input and if they were really strongly against it, I would take that into consideration. But I'm 16, I can figure that out for myself. ... (16 year-old boy)<sup>24</sup>

These somewhat unconcerned comments about “spit” perhaps imply a need to better inform participants about the ways in which their biological samples will be used and the types of genetic and biomarker information that may be uncovered through research. Indeed, one commentator observes, “interviews with children about their participation in genetic susceptibility research indicated that participants' initial positive reaction to participation often reflected an inadequate appreciation of the risks and benefits.”<sup>25</sup>

Relatively few studies have solicited the views of research staff who are responsible for having consent discussions with parents and children and collecting biological samples. One study of nurses involved in a Swedish birth cohort study revealed that those professionals had ethical concerns about appropriate future use of samples:

... there are a lot of samples that exist, both from the parents and from the children, and you [the nurses] thought about how they will be used in the future, for other things than what they are supposed to be used for – there is that possibility. And it is that I have been worried about: their use – even though you don't think they will be used for anything else. That is when you feel a certain anxiety – but I have not heard it from the patients – only from us working with it. I think it is scary ... Samples stand there, frozen down ... for a very long time and ... one can do things with them that were not in the plans from the beginning.<sup>26</sup>

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24 *Supra* note 6.

25 Barbara A. Bernhardt *et al.*, “Parents' and children's attitudes toward the enrollment of minors in genetic susceptibility research: Implications for informed consent” (2002) 116A *American Journal of Medical Genetics* 315.

26 *Supra* note 3 at 75.

The range of investigational activities involved in population genetic birth cohort studies means it is impossible to uniformly categorize the risk involved. Some commentators have argued that “much population-based research involving genetics likely poses minimal risk because it focuses on questions expected to have meaningful public health implications but few clinical implications for individual participants.”<sup>27</sup> If such research involves only minimal risk, then there ought to be no ethical difficulty with parental permission for their child to take part; indeed, “parents consent everyday to the participation of children in sports, in unsupervised play or ear piercing,”<sup>28</sup> activities which involve highly variable degrees of risk. Yet, others have suggested that genetic research exceeds minimal risk because information revealed through investigational tests may “provoke anxiety and confusion, damage familial relationships, and compromise the subjects’ insurability and employment opportunities....”<sup>29</sup>

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27 Laura M. Beskow *et al.*, “Informed Consent for Population-Based Research Involving Genetics” (2001) 286 *Journal of the American Medical Association* 2315 at 2318.

28 Knoppers, *supra* note 9. See also David Wendler *et al.*, “Quantifying the Federal Minimal Risk Standard: Implications for Pediatric Research Without a Prospect of Direct Benefit” (2005) 294 *Journal of the American Medical Association* 826 David Wendler and colleagues have attempted to quantify various risks to which children are exposed in daily life, including being a passenger in a motor vehicle and playing sports. Considering mortality and morbidity risks involved in these activities, they suggest IRBs apply an overly cautious standard when comparing research risks to risks of daily life. See also Celia B. Fisher, Susan Z. Kornetsky & Ernest D. Prentice, “Determining Risk in Pediatric Research with No Prospect of Direct Benefit: Time for a National Consensus on the Interpretation of Federal Regulations” (2007) 7:3 *Am. J. Bioethics* 5. They observe the difference between risks of daily life and research risks: “Some risks in the daily lives of healthy children living in safe environments (e.g. vehicular mortality, serious athletic injuries) are socially permissible because society judges these activities as important opportunities for children’s growth and development. Society may not view these same risks (e.g., mortality, serious physical injury) as minimal when introduced solely for the purpose of producing generalizable knowledge that offers neither the probability of direct benefit to the individual children nor the promise of future benefits for children...” at 7.

29 Jon F. Merz, “Is Genetics Research ‘Minimal Risk’?” (1996) 18:6 *IRB: Ethics and Human Research* 7, quoting Office for Protection from Research Risks,

## Categorizing Risks

It is worth considering these types of risks in further detail. Two types of risks exist: (1) physical risks; and (2) informational privacy risks. Physical risks are generally contemplated by risk categories defined in research ethic guidelines, as they give examples of bodily interventions and the levels of risk they pose. Nonetheless, there is variation in how ethics review bodies perceive the level of physical risk involved in research activities. One study examining categorizations of risks by 188 U.S. institutional review boards (IRBs) found:

A single blood draw was the only procedure categorized as minimal risk by a majority (152 or 81%) of the 188 respondents. An electrocardiogram was categorized as minimal or a minor increase over minimal risk by 100 (53%) and as more than a minor increase over minimal risk by 77 (41%). Allergy skin testing was categorized as minimal risk by 43 IRB chairpersons (23%), a minor increase over minimal risk by 81 (43%), and more than a minor increase over minimal risk by 51 (27%).<sup>30</sup>

Ethics review bodies also have varying opinions on whether genetic research studies constitute minimal or higher risk; one study found that “[e]valuation of risk of the same genetic epidemiology study by 31 IRBs ranged from minimal to high...,”<sup>31</sup> with widely differing levels of review (from expedited to full review) and requirements for consent procedures.<sup>32</sup>

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*protecting Human Research Subjects: Institutional Review Board Guidebook* (Washington, DC: US Department of Health and Human Services, 1993) at 5-43.

30 Seema Shah *et al.*, “How do institutional review boards apply the federal risk and benefit standards for pediatric research?” (2004) 291 *Journal of the American Medical Association* 476. See e.g. Robert M. Nelson & Lainie Friedman Ross, “In Defense of a Single Standard of Research Risk for all Children” (2005) 147 *Journal of Pediatrics* 565 (for further commentary on the four standards of risk set out in the U.S. Code, where the authors advocate replacing the four levels of risk with one standard: the “scrupulous parent” standard). See also David Wendler and Ezekiel J. Emanuel, “What is a “minor” increase over minimal risk?” (2005) 147 *Journal of Pediatrics* 575.

31 Rita McWilliams *et al.*, “Problematic Variation in a Local Institutional Review of a Multicenter Genetic Epidemiology Study” (2003) 290 *Journal of the American Medical Association* 360 at 360.

32 *Ibid.* For example, 32% of IRBs did not require assent of child participants.

Informational risks arise from two possibilities: (1) an unauthorized third party may obtain access to identifiable information; and (2) new information about the participant may be revealed through research activities, such as information about genetic predispositions. In regard to the first risk, the unauthorized person may do nothing with that information or the information may be used to embarrass, stigmatize or discriminate against the individual(s) about whom the information relates. In regard to the second risk, the newly revealed information may be beneficial to the participant (e.g. if it helps the participant take steps to mitigate a disease risk) or it may be harmful (e.g. if it reveals likelihood of developing a serious genetic disease with no prospect of treatment or cure).<sup>33</sup> The probability and magnitude of any of these informational risks materializing is difficult to quantify.

If researchers take appropriate steps to safeguard personal information as required by local law<sup>34</sup> and research ethics rules,<sup>35</sup> then the risk of unauthorized access is less likely to materialize. Risk that inappropriately disclosed information will be used to discriminate against an individual depends also on the existence of legal protections against discrimination<sup>36</sup> and the identity

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33 The harm associated with learning unwelcome genetic information is described by some as a loss of autonomy: see e.g. Graeme T. Laurie, "Challenging Medical-Legal Norms: The Role of Autonomy, Confidentiality, and Privacy in Protecting Individual and Familial Group Rights in Genetic Information" (2001) 22:1 J. Legal Med. 1.

34 See Timothy Caulfield & Nola M. Ries, "Consent, Privacy and Confidentiality in Longitudinal, Population Health Research: The Canadian Legal Context" (2004) Health L.J. Supplement 1 (for discussion of personal information protection laws in Canada and their application to population genetic research).

35 For example, Article 8.6 of the Tri-Council Policy Statement, *supra* note 5, requires that "researchers who propose research involving the banking of genetic material have a duty to satisfy the REB [Research Ethics Board] and prospective research subjects that they have addressed the associated ethical issues, including confidentiality, privacy, storage, use of data and results...."

36 See e.g. *Quebec (Commission des droits de la personne et des droits de la jeunesse) v. Montreal (City)*; *Quebec (Commission des droits de la personne et des droits de la jeunesse) v. Boisbriand (City)* [1999] 1 S.C.R. 381 (Canadian human rights laws prohibit discrimination based on disability and perceived disability. See also Henry T. Greely, "Banning Genetic Discrimination" (2005) 353 *New England Journal of Medicine* 865 and Mark A. Hall & Stephen S. Rich, "Laws Restricting Health Insurers' Use of Genetic Information: Impact on Genetic Discrimination" (2000) 66 *American Journal of Human Genetics* 293 (Some jurisdictions have legisla-

of the unauthorized person. The risks of psychological harm arising from revelation of distressing research results will depend on the extent to which researchers disclose results to participants, a topic discussed in more detail below.

In sum, there is no uniform categorization of risks involved in population genetic cohort studies: physical risks are generally minimal but are occasionally higher depending on the physical intervention involved and privacy risks exist, but the probability and magnitude of privacy harms are difficult to quantify and can be mitigated with appropriate measures. Despite the challenge in categorizing such perils, the risks involved with a child's participation in a birth cohort are critical to issues of consent, notably a parent's right to agree for an infant child to join a long-term study with no anticipated benefits. The following section addresses these issues.

## Parents, Children and Consent to Participate in Birth Cohort Studies

### The Parental Role

As children lack legal capacity, researchers must receive permission from a parent or other authorized representative<sup>37</sup> to recruit a child as a research subject (practically speaking, recruitment into a birth cohort study will involve parental consent at least from the mother<sup>38</sup>). This raises the important question of whether there are legal/ethical restraints on a parent's choice to

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tion that prohibits insurers from using genetic test results and genetic anti-discrimination laws may become more common).

37 For the sake of simplicity, I will use the term "parent" instead of referring to "parent or authorized representative" throughout this article. However, in the absence of a competent parent with legal authority in regard to the child, another authorized representative must make decisions on behalf of the incompetent child. Where a child is in state care, special issues arise regarding the role of child welfare officials in authorizing their wards as research subjects. See e.g. §46.409 C.F.R., *supra* note 15.

38 For ease of reference, I refer to "parent" in the singular form throughout this article as permission from at least one competent parent who has legal authority over a child is necessary. In some cases, researchers may seek (or, depending on applicable legal and ethical rules, be required to obtain) consent from both parents, but in situations of single-parent families, this is not possible.

permit their child's recruitment into a birth cohort study that involves genetic research. First, may the parent permit a child's participation in a cohort study that likely has no benefit for the child? Second, does the parental role change as the child matures and develops independent rights in regard to continued participation in the cohort? Specifically, is there a point at which a mature minor can give legally valid consent to participate or withdraw without parental approval of that choice?

In Canada, the Tri-Council Policy Statement allows an authorized representative to consent for a legally incompetent person to participate in research if the research question can only be addressed with members of the incompetent population and if "[t]he research does not expose them to more than minimal risk without the potential for direct benefits for them."<sup>39</sup> This ethical guidance is subject to legislative provisions that impose specific rules regarding research with incompetent subjects. Quebec's Civil Code, for example, permits an authorized representative to allow a child's participation in research if there are no serious risks and the child does not object.<sup>40</sup> Studies that involve a group of participants, like cohort studies, must have "the potential to produce results capable of conferring benefit to other persons in the same category or having the same disease or handicap."<sup>41</sup>

In the United States, Title 45 of the Code of Federal Regulations recognizes four categories of research with children: (1) research not involving more than minimal risk; (2) research involving more than minimal risk but with the prospect of direct benefit to participants; (3) research involving more than minimal risk, no prospect of direct benefits, but likely to produce generalizable knowledge relevant to the participant's condition; (4) research that would not ordinarily qualify for ethics approval, but which "presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children."<sup>42</sup> In each case, research may be approved for federal funding provided certain conditions are met, including that "adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians...."<sup>43</sup>

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39 Tri-Council Policy Statement, Article 2.5(c), *supra* note 5.

40 *Civil Code of Quebec*, R.S.Q. c. C-1991, Art. 21.

41 *Ibid.*

42 *Supra* note 15.

43 *Ibid.*, §45.404-§45.407.

In Australia, the recently revised *National Statement on Ethical Conduct in Research Involving Humans* permits parental permission for children's participation in research if "it is likely to advance knowledge about" health, welfare or other matters relevant to children and their "participation is indispensable to the conduct of the research."<sup>44</sup> This general rule about children's participation in research does not stipulate that children may only take part in "negligible" or "low" risk research.<sup>45</sup>

The Canadian Tri-Council Policy Statement appears to have the most restrictive rules about parental permission as it limits incompetent children's participation only to minimal risk research, which is defined as research where "the probability and magnitude of possible harms ... are no greater than those encountered by the subject in those aspects of his or her everyday life that relate to the research..."<sup>46</sup> In addition to this limited category of ethically acceptable research, some Canadian commentators also question the legality of parental permission for children to participate in research that does not hold the prospect of direct benefit for the child.<sup>47</sup>

### Parental Motivation to Permit a Child's Participation in Research

In circumstances where a parent may permit her or his child to participate in research, permission should be given voluntarily and with full knowledge and understanding of the nature of the investigational activities and their risks and benefits. However, parents themselves sometimes misunderstand the nature and intent of the research and the rights of research participants. For example, one study about parental decisions to permit a child's partici-

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44 National Health and Medical Research Council, *National Statement on Ethical Conduct in Research Involving Humans* (Canberra: Australian Government, 2007) Article 4.2.4 [Australian National Statement].

45 Unlike other ethics documents, the Australian National Statement does not use the term "minimal risk," but instead defines "negligible" and "low" risk research. See Art. 2.1.6 and 2.1.7, *ibid.*

46 Tri-Council Policy Statement, *supra* note 5, Part C.1. Note that the Québec Civil Code prohibits a minor's participation in research if it poses "serious risk" to health. *Supra* note 40.

47 See e.g. Françoise Baylis & Jocelyn Downie, "An Ethical and Criminal Law Framework for Research Involving Children in Canada" (1993) 1 Health L.J. 39; Bernard Dickens, "The Legal Challenge of Health Research Involving Children" (1998) 6 Health L.J. 131.

pation in a randomized, controlled trial of ibuprofen syrup revealed that a full quarter of parents thought they were obliged to participate.<sup>48</sup>

Several factors influence parents to permit their children to participate in research. Altruism and the desire to advance knowledge to benefit other children in the future is a predominant motivation. In studies involving clinical measures (for example, lung function tests of children involved in asthma research), parents are also motivated by the opportunity to learn health information about their children.<sup>49</sup> Parents with a history of health problems may be more likely to permit their children to participate in studies investigating those health issues, regardless of whether the child has the same condition.<sup>50</sup>

Little empirical research has examined factors that influence parental permission for their minor children's participation in longitudinal, population genetic research. However, in agreeing to participate in long-term research studies, parents may be motivated by the opportunity to receive health information about their children. For example, parents who permitted their infants and young children to be sedated, undergo lung function tests, skin tests and blood draws as part of the Copenhagen Prospective Study on Asthma were motivated by regular access to medical experts and health screening for their children.<sup>51</sup>

In some cases, parents permit their child's participation in research that is not for the child's direct benefit based on the mistaken belief that the research will provide intervention for the child's medical condition. This so-called therapeutic misconception may occur even when parents are told explicitly that a study will not help a child's personal health and will not produce information that is useful and reliable for clinical purposes.<sup>52</sup> Gillam

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48 Margriet van Stuijvenberg *et al.*, "Informed consent, parental awareness, and reasons for participating in a randomised controlled study" (1998) 79 Archives of Disease in Childhood 120.

49 Anne Gammelgaard, Lisbeth Ehler Knudsen & Hans Bisgaard, "Perceptions of Parents on the Participation of their Infants in Clinical Research" (2006) 91 Archives of Disease in Childhood 977; Helen M. Sammons *et al.*, "What Motivates British Parents to Consent for Research" (2007) 7:12 BMC Pediatrics.

50 *Ibid.*

51 Gammelgaard, *supra* note 49.

52 L. Gillam *et al.*, "Enhancing the Ethical Conduct of Genetic Research: Investigating Views of Parents on Including their Healthy Children in a Study on Mild Hearing Loss" (2006) 32 Journal of Medical Ethics 537.



and colleagues explain the ethical problem of therapeutic misconception: "If they [parents] consent to the genetic study on the basis of benefits to their child outweighing the risks to their child, then this is not an informed consent, as there will be, in all probability, no benefits to the child from the information produced at the end of the study."<sup>53</sup> In seeking parental permission for children to participate in cohort studies that are not intended to help a child personally, researchers must emphasize the absence of direct benefit.

### The Child's Assent and Consent

Children's evolving psychosocial maturity poses unique issues for their participation in research; at some point, a child is able to express preferences and make choices about being a research subject. Research into decision-making capacity of minors identifies two key age milestones in cognitive development from childhood to adolescence:

At about the age of 7, the knowledge of children about health and illness reaches a level at which it becomes possible to communicate with them about such matters. ... The second significant turning point comes at about the age of 14 years, when ... a minor has achieved a level of competence in making decisions that differs from that of an adult only in terms of less experience and information and not in terms of ability to make a judgment.<sup>54</sup>

In a study evaluating capacity to consent to medical treatments, 14-year-olds were judged as capable as adults.<sup>55</sup> In regard to participation in research, a study evaluating minor's capacity to consent to an influenza vaccine clinical trial found that children aged six to nine were able to express a preference about participating and asked more questions about risks and benefits as they got older.<sup>56</sup>

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53 *Ibid.* at 540.

54 R. H. Nicholson, ed. *Medical Research with Children: Ethics, Law, and Practice* (Oxford: Oxford University Press, 1986) at 149.

55 Lois A. Weithorn & Susan B. Campbell, "The Competency of Children and Adolescents to Make Informed Treatment Decisions" (1982) 53 *Child Development* 1589.

56 C.E. Lewis, M.A. Lewis & M. Ifekwungue, "Informed consent by children and participation in an influenza vaccine trial" (1978) 68 *Am. Journal of Public Health* 1079.

The World Medical Association states in the Declaration of Helsinki: "When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative."<sup>57</sup> The Canadian Tri-Council Policy Statement also requires researchers to "ascertain the wishes"<sup>58</sup> of incompetent participants when they develop some capacity to understand the research initiative. U.S. rules also require assent.<sup>59</sup> Australia's National Statement does not explicitly require assent, but advises that "even young children with very limited cognitive capacity should be engaged at their level in discussion about the research and its likely outcomes."<sup>60</sup>

In practice, researchers who seek assent from children typically do so beginning around age six or seven, an appropriate age as arguably "[m]ost school-age children possess the capacity to understand what they are being asked to do in the setting of nonbeneficial research (i.e., answer questions or have blood drawn) and to understand that this activity is not something they must do."<sup>61</sup> Diekema describes the importance of assent for children: "The assent requirement reflects the belief that even though some children might not completely understand or consider all the implications of research participation, their level of understanding and decision-making ability are sufficient to decide whether they'd like to participate in an activity that offers no possibility of direct benefit to them."<sup>62</sup> He further identifies four reasons why assent is important: (1) giving children the opportunity to assent to research treats them with dignity and respect; (2) this benefits children's development as autonomous and self-governing individuals; (3) a process of obtaining assent from children reminds parents and researchers that "children are persons with interests and not mere vessels for the purpose of research"; and (4) seeking consent sets an example for children to treat others with respect.

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57 Declaration of Helsinki, *supra* note 5.

58 Tri-Council Policy Statement, *supra* note 5, Article 2.7.

59 C.F.R., *supra* note 15, §46.408.

60 Australian National Statement, *supra* note 44, at 55.

61 Douglas S. Diekema, "Taking Children Seriously: What's so Important about Assent?" (2003) 3:4 American Journal of Bioethics 25.

62 *Ibid.* at 25

Most ethics guidelines emphasize that a child's dissent is definitive in precluding further participation in research.<sup>63</sup> However, Australia's National Statement provides otherwise: "Where a child or young person lacks ... capacity, his or her refusal may be overridden by the parents' judgement as to what is in the child's best interest."<sup>64</sup>

### Mature Minors

As a child matures into adolescence, they typically develop full capacity to weigh options and make choices. The legal concept of a "mature minor" developed in the context of medical treatment to stipulate the circumstances under which a young person can give legally valid consent to treatment independent of a parent or guardian:

... a young person, still a minor, may give, on his or her own behalf, fully informed consent to medical treatment if he or she has sufficient maturity, intelligence and capability of understanding what is involved in making informed choices about the proposed medical treatment. If a young person does not have that degree of maturity, intelligence, and capability of understanding, then that young person cannot give informed consent to proposed medical treatment and consent must be given by a parent or guardian. But once the required capacity to consent has been achieved by the young person reaching sufficient maturity, intelligence and capability of understanding, the discussions about the nature of the treatment, its gravity, the material risks and any special or unusual risks, and the decisions about undergoing treatment, and about the form of the treatment, must all take place with and be made by the young person whose bodily integrity is to be invaded and whose life and health will be affected by the outcome.<sup>65</sup>

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63 See e.g. Tri-Council Policy Statement, *supra* note 5, Art. 2.7 ("The potential subject's dissent will preclude his or her participation") and the MRC Ethics Guide, *supra* note 13 ("If the child does not assent, this should be respected." at 28).

64 Australian National Statement, *supra* note 44, Art. 4.2.14.

65 *Van Mol (Guardian ad litem of) v. Ashmore* 1999 BCCA 6 at para. 75. See also *Re Gillick v. West Norfolk and Wisbech Area Health Authority* [1985] 3 All ER 402 (H.L.) (the leading mature minor case in England, Wales and Northern Ireland, which affirms the same principles as Canadian mature minor case law).

In the treatment context, subject to legislation that overrides the mature minor concept,<sup>66</sup> a young person with the requisite maturity may make even life and death decisions to accept or refuse medical interventions,<sup>67</sup> and no longer requires parental approval of their choices:

At that stage, the parent or guardian will no longer have any overriding right to give or withhold consent. All rights in relation to giving or withholding consent will then be held entirely by the child. The role of the parent or guardian is as advisor and friend. There is no room for conflicting decisions between a young person who has achieved consenting capacity, on the one hand, and a parent or guardian, on the other.<sup>68</sup>

The principles that inform the mature minor doctrine in the context of medical treatment – respect for autonomy and the evolving maturity of a young person - are also relevant in the research context. But ethical and legal rules vary in their recognition of the mature minor concept and a young person who has the maturity and intelligence to understand the nature of a research initiative and related risks and benefits is not necessarily entitled to give or refuse consent to participate without continued parental involvement.

The 1996 version of the Declaration of Helsinki required consent from both the mature minor and an authorized representative,<sup>69</sup> but this requirement did not appear in the 2000 amendments,<sup>70</sup> suggesting that the mature minor's consent alone ought to be sufficient. The U.S. Society for Adolescent Medicine indicates that consent from a mature minor alone is ethically

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66 Child welfare legislation may, in some medical treatment circumstances, override the mature minor concept. See e.g. *B.H. (Next friend of) v. Alberta (Director of Child Welfare)*, 2002 ABQB 371.

67 *Ibid.*

68 *Ibid.*

69 The 1996 version stated, at s. 11: "Whenever the minor child is in fact able to give consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian." World Medical Association, *Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects (Declaration of Helsinki)* (Somerset West, Republic of South Africa: 48<sup>th</sup> WMA General Assembly, 1996).

70 Section 25 of the 2000 version states that a minor's *assent* must be accompanied by consent from an authorized representative. Declaration of Helsinki, *supra* note 5.

permissible in some circumstances involving minimal risk or greater than minimal risk if there is a prospect of direct benefit to the minor.<sup>71</sup> The U.S. Federal Code provides waiver of parental permission in some cases and the mature minor doctrine may also exclude a requirement for parental permission in some situations.<sup>72</sup> However, IRBs in the U.S. have variable opinions about the acceptability of obtaining consent only from a minor:

Over one-half of IRBs supported [the opportunity for] minors to provide informed self-consent for seven of 10 general research categories: anonymous surveys (supported by 93%), research involving sensitive material if nothing more than survey (89%) or venipuncture (53%) were involved, and research on diseases for which minors may consent to treatment including survey (93%), venipuncture (68%), or medication approved for use in pediatric patients (57%).<sup>73</sup>

In Canada, the Tri-Council Policy Statement stipulates that if a research participant attains legal competence during the course of a research study, researchers must obtain their informed consent “as a condition of continuing participation,”<sup>74</sup> but is silent on whether that consent alone is sufficient for a mature minor. The Tri-Council Policy Statement cautions that “[t]he law on competence varies between jurisdictions. Researchers must comply with all applicable legislative requirements.”<sup>75</sup>

In both Canada and the United Kingdom, the common law is unclear on the application of the mature minor principle in the research context as the matter has not been litigated. The U.K. Medical Research Council Ethics

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71 For discussion, see Society for Adolescent Medicine, *Guidelines for Adolescent Health Research* (2003) 33 *Journal of Adolescent Health* 410.

72 For discussion, see Lainie Friedman Ross, “Informed Consent in Pediatric Research” (2004) 13 *Cambridge Quarterly of Healthcare Ethics* 346.

73 K.A. Mammel & D.W. Kaplan, “Research consent by adolescent minors and institutional review boards” (1995) 17 *Journal of Adolescent Health* 323.

74 Tri-Council Policy Statement, *supra* note 5, Art. 2.6(d).

75 Tri-Council Policy Statement, *supra* note 5, at Section E. Québec’s Civil Code does not recognize a mature minor doctrine for the purposes of research participation. *Supra* note 40. For further discussion, see Michael Hadskis, “The Regulation of Human Biomedical Research in Canada” in Jocelyn Downie, Timothy Caulfield & Colleen Flood, eds. *Canadian Health Law and Policy*, 3<sup>rd</sup> ed. (Markham, ON: LexisNexis Canada, 2007) at 257.

Guide notes that the mature minor doctrine “might reasonably be applied [to research], although the threshold for [a minor’s required level of] understanding will vary according to the complexity of the research.”<sup>76</sup> A Canadian legal commentator similarly suggests that “courts may well hold [the mature minor doctrine applies to research], at least for research with anticipated benefits to the participants.”<sup>77</sup> It is arguable that if the law accepts that minors can be mature enough to make independent medical decisions, extending to situations with grave health consequences, then the law should also recognize that many minors develop sufficient maturity to make choices about research participation. Children who grow up as research subjects in a birth cohort study are even more likely to develop competence to make their own choices as adolescents because they will likely have considerable exposure to research settings and staff (e.g. through clinic and home visits) and ongoing opportunities to raise questions about and understand what it means to be a research participant.<sup>78</sup>

Australia’s National Statement provides for explicit recognition of the mature minor doctrine in specified circumstances: “An ethical review body may approve research to which only the young person consents if it is satisfied that he or she is mature enough to understand and consent, and not vulnerable through immaturity in ways that would warrant additional consent from a parent or guardian.”<sup>79</sup> Interestingly, these guidelines permit a child who is capable of giving consent, but still “vulnerable because of relative immaturity in other respects” to consent without parental involvement provided the research is low risk, the research aims to benefit the group to which the participant belongs and the participant is either estranged from his/her parent or “it would be contrary to the best interests of the young person to seek consent from the parents, and provision is made to protect

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76 MRC Ethics Guide, *supra* note 13, at 23-24.

77 Hadskis, *supra* note 75 at 295.

78 Despite these arguments, some commentators suggest that researchers and parents abdicate their ethical responsibilities if they believe that consent from a minor alone is sufficient for their participation in research. See Lainie Friedman Ross, *supra* note 72, at 350-352. She cites Ackerman’s contention that “we fool ourselves if we argue that we have fulfilled our moral duty by standing aside and asking the child to decide” (quoting T.F. Ackerman, “Fooling ourselves with child autonomy and assent in nontherapeutic clinical research” (1979) 27 *Clinical Research* 345).

79 Australian National Statement, *supra* note 44, Art. 4.2.8.

the young person's safety, security and wellbeing in the conduct of the research."<sup>80</sup>

Before the 2007 amendments, Australia's National Statement made no allowance for consent from a mature minor,<sup>81</sup> an omission that attracted forceful criticism.<sup>82</sup> Advocates of adopting the mature minor doctrine in research argued that the requirement of obtaining parental consent for any participant under age 18 was "out of step with international practice" and possibly unethical as it bars some young people from research participation (e.g. those who are estranged from parents or who do not want parents to know they are participating in certain types of research, such as studies related to sexual activity, drug/alcohol use, or other topics likely to be of particular sensitivity for adolescents). As described above, the 2007 Australian National Statement addresses these criticisms and provides a useful model for other jurisdictions.

### Managing Assent and Consent in Birth Cohort Studies

If children are recruited into population genetic cohort studies in infancy or early childhood, researchers must develop procedures for seeking assent and consent from individual participants as they mature and become capable of expressing their own preferences and making autonomous choices. In the absence of assent and consent, "participants enrolled as children will be denied the opportunity for an independent decision regarding research participation based on the participant's own review of information about study procedures and goals."<sup>83</sup> Research initiatives that involve periodic contact with children and their families to gather new biological samples and information provide natural opportunities to discuss assent and consent as the child matures. Some cohort studies (for example, the US National Children's

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80 *Ibid.*, Art. 4.2.9.

81 See National Health and Medical Research Council, *National Statement on Ethical Conduct in Research Involving Humans* (Canberra: National Health and Medical Research Council, 1999).

82 See e.g. Lena A. Sanci *et al.*, "Youth health research ethics: time for a mature-minor clause?" (2004) 180 *Medical Journal of Australia* 336; Dagmar M. Hallor *et al.*, "Practical evidence in favour of mature-minor consent in primary care research" (2005) 183:8 *Medical Journal of Australia* 439.

83 Wylie Burke & Douglas S. Diekema, "Ethical Issues Arising from the Participation of Children in Genetic Research" (2006) 149 *Journal of Pediatrics* S34.

Study<sup>84</sup>) manage this issue by seeking assent and/or consent from participants at specified intervals, typically ages 7 and 14.

Researchers must also develop age-appropriate materials to explain the cohort study to children and, importantly, their rights as participants. Minors may have variable levels of understanding about different aspects of research participation. One study found that children ranging from ages five to 12 could understand information about the purpose of and procedures involved in psychological research not intended for direct benefit, but they had comparatively weaker comprehension of risks, benefits and the voluntary nature of research.<sup>85</sup> Indeed, a primary concern in obtaining voluntary assent or consent from children is “younger children’s tendency to agree with influential adults and to not ask questions unless they are encouraged to do so.”<sup>86</sup> Children aged ten and younger may also have difficulty understanding that research is not intended to help them directly, but aims to enhance generalizable knowledge.<sup>87</sup> Depending on available resources, researchers may use interactive tools to help minors understand their rights and options. The US National Children’s Study is piloting a computerized tool that tests participants’ understanding of various aspects of the research and replays explanatory information if a participant enters an incorrect answer.<sup>88</sup>

### Conflicting Views between Parents and Minors

Parents and minors may have conflicting views over whose choice should prevail in regard to research participation, especially in early adolescence where the child may assert greater desire to make independent choices.<sup>89</sup> Not very surprisingly, parents often “are relatively poor judges of children’s

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84 National Children’s Study E-Updates, “The National Children’s Study Develops New Informed Consent Tool” (August 2007), online: <[http://www.nationalchildrensstudy.gov/news/e-updates/e\\_update\\_08102007.cfm](http://www.nationalchildrensstudy.gov/news/e-updates/e_update_08102007.cfm)>.

85 Rona Abramovitch *et al.*, “Children’s Capacity to Consent to Participation in Psychological Research: Empirical Findings” (1991) 62 *Child Development* 1100.

86 *Supra* note 6.

87 E.D. Nannis, “Children’s understanding of their participation in psychological research: Implications for issues of assent and consent” (1991) 23 *Canadian Journal of Behavioural Science* 133.

88 *Supra* note 84.

89 J.L. Brody *et al.*, “Family and Physician Influence on Asthma Research Participation Decisions for Adolescents: The Effects of Adolescent Gender and Research Risk” (2006) 11 *Pediatrics* e356.



developmental stage, and thus of their ability to understand explanations of an illness or event.”<sup>90</sup> In contrast, some studies suggest adolescents are more willing to participate in above minimal risk research than parents are in giving permission for minors’ participation.<sup>91</sup> In a study examining the views of 10 to 16 year olds on participation in research on genetic susceptibility to disease, most minors expressed a desire to decide for themselves: “The general view was that they should have control over anything that involves them. ‘...It’s my doing, my actually giving the spit and them actually doing the research on my spit ... so it should be my choice.’ (16-year-old).”<sup>92</sup>

In situations of conflicting views between parent and child, the dissenting decision generally prevails.<sup>93</sup> Even if a minor is considered mature enough to make an independent choice and wishes to participate in research, parental opposition would generally dissuade researchers from including the minor. Further, in jurisdictions that lack clarity regarding the application of the mature minor doctrine in research, researchers may act unlawfully if they accept a mature minor’s consent in the face of parental disapproval.

However, if a child has been in a longitudinal study since birth or early childhood and, when the child reaches adolescence, the parents wish to withdraw their participation but the child’s choice is to continue, researchers may want to accept the child’s ongoing participation. Considering the costs of losing a participant after a decade or more of data collection, researchers may still wish to include the child despite parental disapproval provided the child is able to fulfill study requirements without reliance on their parent (e.g. for transportation to a study centre). If the legal and ethical appropriateness of doing so is unclear, researchers ought to seek advice from an ethical review body and legal counsel. In the converse situation where a parent would like a child to continue participating but the child expresses a desire to discontinue, a parent is unlikely to force the child against their wishes and failing to respect the mature minor’s objection is contrary to ethics guidelines reviewed here.

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90 *Supra* note 6.

91 J.L. Brody *et al.*, “Comparisons of adolescent and parent willingness to participate in minimal and above-minimal risk pediatric asthma research protocols” (2005) 37 *Journal of Adolescent Health* 229.

92 *Supra* note 6.

93 *Ibid.*

## The Right to Withdraw from Research

The right to withdraw from research is a key aspect of the right to give ongoing, knowledgeable consent and research participants may choose to withdraw from research at any time without reprisal.<sup>94</sup> In long-term population genetic studies, withdrawal raises questions in regard to continued use of previously collected biological samples and personal information about research subjects. On withdrawal, a participant may request that biological samples and personal information collected to that point be withdrawn from further research or may authorize continued use (but no further contact with the withdrawing participant). However, information and samples that have already been processed in some way and aggregated into research studies clearly cannot be separated and removed.

As minors involved in cohort studies reach an appropriate age and maturity to express choices about their continued participation, researchers must explain withdrawal rights and options to them. Fisher suggests that some children may have difficulty understanding privacy issues associated with long-term storage and use of biological samples and personal information:

Informing guardians about planned uses for stored data on participant withdrawal does not resolve privacy concerns for the children involved. First, in studies initiated prenatally or at birth, the child has no role in the participation decision. Children and young adolescents informed during re-consent procedures about plans for future use of collected data have neither the mature cognitive skills nor the experience to understand the privacy implications of such policies. In appreciation of the unique nature of children's research, it may be ethically appropriate to permit the withdrawal of data held in data banks at the participant's request. This policy need not extend indefinitely. Rather, the right of participants to withdraw their data might be extended only until they reach the age of majority or until the study has been completed and data anonymized.<sup>95</sup>

On this view, if a child chooses to withdraw from participation, then researchers should not attempt to obtain consent for continued use of stored

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94 Declaration of Helsinki, *supra* note 5, Principle 22.

95 Celia B. Fisher, "Privacy and Ethics in Pediatric Environmental Health Research – Part II: Protecting Families and Communities" (2006) 114 *Environmental Health Perspectives* 1622.

data as the implications of this use may be too obscure for a minor to comprehend. However, this suggests that researchers may contact the person when she or he reaches the age of legal majority to request permission to re-access the data. Several difficulties arise with this suggestion. First, if the young person is unable to understand the implications of storage and future use of their samples and information, then it is debatable whether they are mature minors for the purpose of consenting to such research and parental/guardian permission may still govern. Second, if the minor's request to withdraw is respected and researchers agree not to use existing samples and information pertaining to that (ex-)participant, then future contact may itself constitute a privacy breach unless s/he gives permission to be contacted in the future. Third, this assumes that researchers retain the biological samples and other information for the prospect of future use, rather than destroying it or permanently anonymizing it.

If a mature minor decides s/he does not want to continue participating in a cohort study, but the parent (typically the mother) is willing to continue, the problem of "informational entanglement" arises. As Holm points out, banked biological samples, such as placental tissue, may contain information about both the mother and child.<sup>96</sup> As right trumps preference, he convincingly argues that the mature minor's right to withdraw prevails over the parent's preference to continue. Although conflicts of this nature may be relatively rare, researchers should be prepared to manage them.

### **The Complexities of Reporting: Ethical and Legal Issues in Handling Information**

Longitudinal research initiatives with pediatric populations raise ethical and legal quandaries related to reporting results to families. Fisher describes several disconcerting examples:

... what should investigators do if they discover that a child in a normal control group has a biologic marker for an untreatable disease that typically emerges in early adulthood? What should families or the child be told if blood tests indicate that a 10-year-old research participant has been exposed to levels of an environmental toxicant associated with sterility? What if a misattributed paternity is discov-

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96 Soren Holm, "Informed Consent and Bio-banking of Material from Children" (2005) 1:1 *Genomics, Society and Policy* 16.

ered indicating that a child participant is not at risk for the health problem for which he or she was recruited into the study?<sup>97</sup>

Research participants, including parents who agree to their children's participation, have mixed views on return of results. Those who mistakenly believe that research will directly benefit the child typically want to receive results of investigational tests. Even a proportion of those who understand that results may have no clinical utility still express a desire to receive the information. This may stem from simple curiosity, a sense of parental obligation (i.e. a dutiful parent should be interested in learning information about the child), or a belief that the information may become clinically relevant in the future. Others, in contrast, do not want to be troubled by results whose implications cannot presently be understood.

The Tri-Council Policy Statement provisions regarding genetic research state simply that researchers shall report results "if the individual so desires."<sup>98</sup> UNESCO's *International Declaration on Human Genetic Data* states that genetic research participants (and patients having clinical genetic tests) have "the right to decide whether or not to be informed of the results."<sup>99</sup> A recent review of international ethical norms regarding return of research results concludes that results that "meet the requirements of scientific validity, clinical significance, [and] benefit (ie existence of prevention or treatment)" ought to be disclosed to participants, subject to a participant's "explicit refusal to know."<sup>100</sup>

97 Celia B. Fisher, "Privacy and Ethics in Pediatric Environmental Health Research – Part I: Genetic and Prenatal Testing" (2006) 114 *Environmental Health Perspectives* 1617.

98 Tri-Council Policy Statement, *supra* note 5, Art. 8.1.

99 UNESCO, *International Declaration on Human Genetic Data*, Article 10 (16 October 2003), online: UNESCO <[http://portal.unesco.org/en/ev.php-URL\\_ID=17720&URL\\_DO\\_TOPIC&URL\\_SECTION=201.html](http://portal.unesco.org/en/ev.php-URL_ID=17720&URL_DO_TOPIC&URL_SECTION=201.html)>:

When human genetic data, human proteomic data or biological samples are collected for medical and scientific research purposes, the information provided at the time of consent should indicate that the person concerned has the right to decide whether or not to be informed of the results. This does not apply to research on data irretrievably unlinked to identifiable persons or to data that do not lead to individual findings concerning the persons who have participated in such a research. Where appropriate, the right not to be informed should be extended to identified relatives who may be affected by the results.

100 Bartha Maria Knoppers *et al.*, "The emergence of an ethical duty to disclose genetic research results: international perspectives" (2006) 14 *European Jour-*

In practice, researchers typically adopt a policy of not returning clinically uncertain results to participants, partly due to ethical complexities of disclosing such information and also logistical challenges and expense. As Burke and Diekema state: “Unless a study procedure or test is proven to be valid, and knowledge of the result would allow a therapeutic opportunity of demonstrated benefit, researchers have traditionally not provided participants with personal results of tests done exclusively for study purposes. Instead, participants learn about study outcomes through reports or publications of aggregate data.”<sup>101</sup>

In some cases, researchers return results of routine tests to participants (e.g. iron deficiency tests) that can be interpreted in a clinically meaningful way. Results may be sent directly to participants with an explanatory letter or to a participant’s physician. In the context of pediatric cohorts, researchers should be careful to emphasize that a child’s participation in investigational studies cannot replace visits to a physician or other health care provider.

Interestingly, some birth cohort studies have revised their initial policies about return of results, particularly where a blanket policy against reporting any result became problematic as the research progressed. The Avon Study of Parents and Children began with a policy that no results would be reported based on concerns about “whether participants would want unsolicited bad news.”<sup>102</sup> However, after several studies started to produce results, the non-reporting policy was amended:

... in cases of clinical testing where the abnormal findings would be immediately available – for example, in tests of vision or hearing – the policy of non-disclosure should be abandoned and the parents given access to relevant information. In any case where the

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nal of Human Genetics 1170. See also Vardit Ravitsky & Benjamin S. Wilfond, “Disclosing Individual Genetic Results to Research Participants” (2006) 6:6 Am. Journal of Bioethics 8; Gaile Renegar *et al.*, “Returning Genetic Research Results to Individuals: Points-to-Consider” (2006) 20:1 Bioethics 24; Carolyn Johnston & Jane Kaye, “Does the UK Biobank have a Legal Obligation to Feedback Individual Findings to Participants?” (2004) 12 Med. L. Rev. 239 (for further analysis of returning results of genetic research),

101 *Supra* note 83.

102 S.E. Mumford, “Children of the 90s: Ethical Guidance for a Longitudinal Study” (1999) 81 Archives of Disease in Childhood, Fetal & Neonatal Edition F146 at F150.

research was intended to detect conditions that posed serious reversible threats to health and these conditions might not manifest contemporaneous clinical symptoms the research would have to be planned in such a way as to permit parents to be notified.<sup>103</sup>

Some ethics guidelines impose specific obligations on researchers to develop policies regarding return of results, particularly in the context of genetic research. The Australian National Statement provides: "Where research may discover or generate information of potential importance to the future health of participants, or their blood relatives, researchers must prepare and follow an ethically defensible plan to disclose or withhold that information."<sup>104</sup> A defensible plan "must take into account the clinical relevance of the research information, the types of genetic test used in the research, and the results of those tests."<sup>105</sup> These ethics guidelines recognize a participant's right to choose not to receive information,<sup>106</sup> but oblige researchers "to confirm this decision [with the participant] when the results of the research are available." The guidelines also emphasize the importance of genetic counseling for participants to help them understand research results that are disclosed to them and the need to clearly explain the difference between research and clinical tests.<sup>107</sup>

In seeking consent from minors when they attain sufficient capacity to exercise choices about their research participation, researchers should address minors' preferences about return of results. Some commentators have expressed concern about providing genetic test results to minors due to concerns about psychological ramifications.<sup>108</sup> Some studies – predominantly of adults – report mixed results on whether individuals who learn of elevated genetic risk status display increased stress and anxiety, though one system-

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103 S.E. Mumford, "Children of the 90s II: Challenges for the Ethics and Law Committee" (1999) 81 Archives of Disease in Childhood, Fetal & Neonatal Edition F228 at F231.

104 Australian National Statement, *supra* note 44, Art. 3.5.1.

105 *Ibid.*, Art. 3.5.2.

106 *Ibid.*, Art.3.5.2(a)(i) states that the plan for return of results should "enable participants to decide whether they wish to receive the information and who else may be given the information."

107 *Ibid.*, Art. 3.5.3.

108 For discussion of this issue, see e.g. Timothy Caulfield & Bartha Maria Knoppers, "Genetic Testing, Legal Capacity and Adolescents" (1998) 6 Health L.J. 115.

atic review of psychological consequences of predictive genetic testing found no long-term impacts:

The studies reviewed found no evidence of abnormally high levels of, nor increases in, emotional distress in mutation carriers or non-carriers at any point during three years after predictive genetic testing. Both carriers and noncarriers showed decreased distress after testing, with this being greater and more rapid amongst non-carriers. Test result (ie being a carrier or non-carrier) was rarely predictive of distress more than one month after testing, in contrast with pre-test emotional state which was a stronger predictor.<sup>109</sup>

Studies focusing specifically on the impact of predictive genetic testing on children indicate that most do not experience clinically significant psychological distress.<sup>110</sup> One recent Finnish study investigated adolescents' decision-making when offered a predictive test for a genetic mutation associated with a 95% risk of developing diabetes.<sup>111</sup> Twenty-nine of 39 adolescents (12 to 18 years of age) approached agreed to the testing and nine were found to carry the mutation. A small majority (55%) preferred to receive the results in the absence of parental involvement and three-quarters were satisfied with their decision to be tested, though 25% were dissatisfied or upset. Of those who returned a follow-up questionnaire one year later (21

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109 Marita Broadstock, Susan Michie & Theresa Marteau, "Psychological Consequences of Predictive Genetic Testing: A Systematic Review" (2000) 8 *European Journal of Human Genetics* 731 at 735. See e.g. Roger T. Anderson *et al.*, "Impact of hemochromatosis screening in patients with indeterminate results: The hemochromatosis and iron overload screening study" (2006) 8:11 *Genetics in Medicine* 681 (clinically uncertain results may be more likely to provoke anxiety, especially where subjects misunderstand an uncertain result as meaning they are more likely to develop disease).

110 Susan Michie, M. Mobrow & Theresa Marteau, "Predictive genetic testing in children and adults: a study of emotional impact" (2001) 38 *Journal of Medical Genetics* 519; A.M. Codori *et al.*, "Genetic testing for hereditary colorectal cancer in children: long-term psychological effects" (2003) 116 *American Journal of Medical Genetics* 117 and A.M. Codori *et al.*, "Genetic testing for cancer in children: Short-term psychological effect" (1996) 150:11 *Archives of Pediatrics and Adolescent Medicine* 113.

111 Brita Liljeström *et al.*, "Adolescents at Risk for MODY3 Diabetes Prefer Genetic Testing Before Adulthood" (2007) 30 *Diabetes Care* 1571.

of the original 29), all but one “correctly reported their test result and its interpretation”, suggesting that adolescents have the capacity to understand the meaning of predictive genetic testing. The authors, however, caution that “adolescents may be more disposed to ‘natural optimism’, in that they understand but do not necessarily internalize the risk of ...” disease. These studies on the impact of testing on minors emphasize the importance of pre- and post-test counseling.

In birth cohort studies, policies about return of results must be explained clearly during the initial consent process to ensure parents have an accurate understanding of the type of results – if any – that will be reported to them and the manner in which they will be reported.<sup>112</sup> As children develop capacity to make independent choices as research subjects, researchers ought to discuss with them their preferences about receiving results and, with appropriate counseling, it is unlikely that adolescents will experience major psychological problems from learning new medical information about themselves.

### Legal and Ethical Issues Arising from Family and Home Studies

Some pediatric cohort studies involve visits to the child’s home to gather data of environmental exposures, such as collection of house dust samples, radon gas measurements, and room temperature readings. Investigations that reveal risk of harm to the child may give rise to a duty to warn. A US research institute studying the effectiveness of various lead abatement measures was sued in 2001 for allegedly failing to warn parents of the risks to their children of living in a home with excessive levels of lead exposure.<sup>113</sup> The Court ruled that parents consented to participate with their children in the study based on the understanding that researchers would inform them:

of all the information necessary for the subject to freely choose whether to participate, and continue to participate, and receive promptly

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112 Potential participants should also be informed of mechanisms that may be used to communicate general research findings, such as newsletters or websites.

113 *Grimes v. Kennedy Krieger Institute Inc.* 366 Md 29 (2001) online: Maryland Judiciary <http://www.courts.state.md.us/opinions/coa/2001/128a00.pdf> [*Grimes*]. For discussion, see e.g. Leonard H. Glantz, “Nontherapeutic Research with Children: *Grimes v. Kennedy Krieger Institute*” (2002) 92 *American Journal of Public Health* 1070 and M. Spriggs, “Canaries in the mines: children, risk, non-therapeutic research, and justice” (2004) 30 *Journal of Medical Ethics* 176.



any information that might bear on their willingness to continue to participate in the study. This includes full, detailed, prompt, and continuing warnings as to all the potential risks and hazards inherent in the research or that arise during the research.<sup>114</sup>

In addition to revealing potentially harmful environmental exposures, home visits may unexpectedly reveal signs of abuse, neglect or other harms to a child. In interviews with new mothers and their partners, researchers may develop concerns about serious post-partum depression or learn information about spousal violence. The Avon Study of Parents and Children addressed these concerns as follows:

A partial solution was the study's decision to set up a telephone hotline ... to facilitate [access to support services]. A comprehensive list was compiled of sources of assistance, from general practitioners to rape crisis centres, and at the end of each questionnaire, participants were encouraged to consult the hotline for information or to speak to their own doctor or health visitor if they had questions. Interviewers who encountered very distressed mothers were also advised to encourage them gently to seek whatever assistance was felt necessary from appropriate sources.<sup>115</sup>

In situations of suspected child abuse or neglect, researchers may have a legal duty to report information to child protection services and participants should be informed of this obligation during the consent process so they are aware that confidentiality promises are limited by overriding duties to protect children from harm. Laws in some jurisdictions require "any person" who believes a child needs protection to report to protective agencies, while other laws impose mandatory reporting only on specified categories, such as physicians or other professionals who work with children.<sup>116</sup> Researchers

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114 *Grimes, ibid.* at 63.

115 *Supra* note 102 at F148.

116 Almost all Canadian jurisdictions impose reporting duties on "any person": see e.g. *Child, Youth and Family Enhancement Act*, R.S.A. 2000, c.C-12, s.4(1) and *Child, Family and Community Service Act*, R.S.B.C. 1996, c.46, s.14(1). In the United States, mandatory reporting obligations apply only to certain categories of individuals, including physicians, domestic violence workers, commercial film or photograph processors and members of the clergy, but researchers may report

who are not explicitly mandated by law to report may still exercise discretion to report suspected cases of abuse or neglect and research ethics boards and funding agencies “are tending to interpret reporting laws as applying to researchers, including requiring that research subjects are informed of this responsibility in consenting procedures.”<sup>117</sup>

Some researchers, particularly those involved in studies involving higher-risk families or communities, express concern that reporting to protective services may have a chilling effect on research participation: “...study participants may not respond candidly to questions about child rearing, the use of physical discipline, or possible maltreatment experience, fearing that doing so may lead to CPS [child protective services] investigations of themselves or their families.”<sup>118</sup> However, situations of abuse or neglect arise very rarely in research studies, even in higher risk populations.<sup>119</sup> Depending on the sensitivity of the circumstances, researchers may discuss their concerns with the family and inform them of their duty to report to protective services. Reporting may not necessarily cause the participating parent to withdraw their child from the study, as one study found that “[d]iscussing the need to make a report with the primary caregiver prior to doing so may have minimized the potential negative impact on participant trust in the researchers and the project.”<sup>120</sup>

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on a discretionary basis. For further information, see Child Welfare Information Gateway, “Mandatory Reporters of Child Abuse and Neglect: Summary of State Laws” (March 2005), online: Child Welfare Information Gateway <[http://www.childwelfare.gov/systemwide/laws\\_policies/statutes/mandaall.pdf](http://www.childwelfare.gov/systemwide/laws_policies/statutes/mandaall.pdf)>. See also A.M. Steinberg *et al.*, “Are Researchers Bound by Child Abuse Reporting Laws?” (1999) 23 Child Abuse Neglect 771.

117 Steinberg, *ibid.* at 771.

118 Elizabeth Dawes Knight *et al.*, “Reporting Participants in Research Studies to Child Protective Services: Limited Risk Attrition” (2006) 11 Child Maltreatment 257 at 258.

119 One study found that only 17 child protection reports were made out of 1354 families involved in the U.S. Longitudinal Studies of Child Abuse and Neglect. Protective service agencies accepted nine of the 17 reports for further investigation. *Ibid.*

120 *Ibid.* at 261.

## Conclusion

Longitudinal population genetic research that follows cohorts of subjects from birth to the teen years or even older can provide tremendously valuable insights into the origins, prevention and treatment of childhood and some adult onset diseases. One genetic researcher argues:

Studies need to take account of environmental influences in the widest sense (nutrition, physical and noxious exposures, infections and psychosocial challenges), gene-gene interactions and probably transgenerational effects as well. This is easier said than done, and only makes economic and scientific sense as part of a comprehensive general population (pre-) birth cohort with high-quality measurements.<sup>121</sup>

Added to scientific and financial challenges, such research raises unique legal and ethical issues that must be addressed early in the design of research initiatives. Uncertainties and ambiguities stem from three sources: inconsistent perceptions and categorizations of risks present in longitudinal cohort studies involving genetic research; variable approaches across jurisdictions to the regulation of children's participation in research; and lack of legal precedent and clarity in areas such as parental rights to permit their child's participation in research without direct benefit and the rights of mature minors in research.

Researchers involved in planning and running birth cohort studies that involve genetic research must navigate this somewhat uncertain ethical and legal terrain and ensure fundamental rights of research participants are respected. Developing procedures for obtaining informed, voluntary research participation is critical – first in the form of parental or guardian permission and later assent and consent from children as they develop capacity to make independent choices. Because researchers typically have repeated contact with parents and children over the course of a longitudinal study, they can ensure consent is an ongoing process and that children can exercise their own rights to continue or withdraw from participation.

Researchers - and ethics boards tasked with reviewing proposals for population genetic birth cohort studies - must be knowledgeable about applicable ethics rules and legal principles that create obligations in diverse

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121 M. Pembrey, "Genetic Epidemiology: Some Special Contributions of Birth Cohorts" (2004) 18 Paediatric and Perinatal Epidemiology 3 at 3.

areas including consent to participate, rights to withdraw, confidentiality obligations and duties to report. Where local guidelines are ambiguous or silent on specific issues, reference to ethics statements from other jurisdictions may be useful in developing defensible policies.

**Table 1: Pediatric Population Genetic Initiatives**

Study	Location	Goal of Study	Number of Subjects
The National Children's Study	United States  <i>Mandated by Children's Health Act, 2000</i>	Study effects of environmental influences on children's health and development	More than 100,000 children across the United States, following them from pre-birth to age 21
Project Viva	Boston, United States	Examine role of prenatal and perinatal factors in outcomes of pregnancy, infancy and childhood	Over 2000 pregnant women and their children – recruitment during pregnancy to assess maternal and fetal outcomes
Tucson Children's Respiratory Study	Tucson, United States	Long-term, longitudinal, prospective study of risk factors for acute lower respiratory tract illnesses	Approx 1200 healthy newborns recruited between 1980 and 1984 Just over 60% still enrolled by age 16
Children's Hospital of Philadelphia Center for Applied Genomics	Philadelphia, United States	Investigate genetic links to common childhood diseases (asthma, diabetes, obesity) and pediatric cancer; focus on development of therapies targeted to a child's genetic profile	Analysis of DNA samples stored from 100,000 children over 3 years; DNA will be scanned for approximately 550,000 common markers; samples linked with medical records in triple-encrypted database to protect patient identity from researchers
Autism Genome Project	National Alliance for Autism Research and the National Institutes of Health, United States with international collaborators	Large-scale, collaborative genetics research project designed to map the human genome to identify autism susceptibility genes	Approximately 1200 multiplex families (two children with autism spectrum disorders and their parents) from all over the world who are directly affected by autism spectrum disorders
Avon Longitudinal Study of Parents and Children (also referred to as "Children of the 90s" study)	England	Understand interaction between physical and social environments with genotype to influence children's health, behavior and development	14,000 babies born between April 1991 and December 1992 in the Bristol area of England; recruitment of mothers during pregnancy and children followed to age 7 and beyond

**Table 1: Pediatric Population Genetic Initiatives *cont.***

<b>Study</b>	<b>Location</b>	<b>Goal of Study</b>	<b>Number of Subjects</b>
Canadian Healthy Infant Longitudinal Development (CHILD) Study	Canada	Study environment and biological factors linked with allergy and asthma	Proposed sample of 10,000 children and their parents, followed from birth to age five
Copenhagen Prospective Study on Asthma in Childhood	Denmark	Investigate relationships among genetic, environmental, and lifestyle factors in the development of atopic diseases in high-risk children	411 children born to asthmatic mothers between 1998 and 2001
Danish National Birth Cohort	Copenhagen	Investigate short and long term health impacts of prenatal and childhood exposures, including infections, diet and other environmental factors	At Aug 2000, 60,000 pregnant women recruited
All Babies in South-east Sweden (ABIS)	Sweden	Investigate Type 1 diabetes and other immune-mediated diseases	17 005 children and their families recruited from all births between October 1997 and October 1999 in the southeast region of Sweden; follow for first six years of child's life and likely longer

**Table 2: Select Ethics Guidelines Regarding Minors' Participation in Research**

	<p><b>CANADA</b> Tri-Council Policy Statement – Ethical Conduct for Research Involving Humans (amended to 2005)</p> <p><b>Section 5: Inclusion in Research</b> “... some have argued that the principle of free and informed consent means that only competent individuals should be permitted to participate in research that would likely be harmful or of no benefit to them. Strict application of such a principle would deny incompetent individuals many of the benefits of research participation....” “... age has been used unfairly to exclude individuals from participation in research. The result of such exclusion is that insufficient research has been done on the young....” <b>Art. 5.3:</b> “[Subject to consent provisions] those who are not competent to consent for themselves shall not be automatically excluded from research that is potentially beneficial to them as individuals, or to the group that they represent.”</p>	<p><b>UNITED STATES</b> Code of Federal Regulations</p> <p>No general statements about inclusion of children in research. <b>§46.402: Definitions</b> <b>Children</b> are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.</p>	<p><b>UNITED KINGDOM</b> Medical Research Council Ethics Guide – Medical Research Involving Children (2004)</p> <p><b>1.3.</b> Children require special protection because they are less likely than adults to be able to express their needs or defend their interests – they may not have the capacity to give consent. Research should only include children where the relevant knowledge cannot be obtained by research in adults [and] The purpose of the research is to obtain knowledge relevant to the health, wellbeing or healthcare needs of children. <b>2.</b> Medical research involving children is essential for advancing child health and wellbeing.</p>	<p><b>AUSTRALIA</b> National Health and Medical Research Council, National Statement on Ethical Conduct in Research Involving Humans (2007)</p> <p><b>4.2.4.</b> When children and young people are not of sufficient maturity to consent to participation in research, it is justifiable to involve them only when: (a) it is likely to advance knowledge about the health or welfare of, or other matters relevant to, children and young people; or (b) children’s or young people’s participation is indispensable to the conduct of the research.</p>
<p><b>Inclusion of children</b></p>				

<p><b>Risk</b></p>	<p><b>C.1. Minimal Risk</b>          "The standard of minimal risk is commonly defined as follows: if potential subjects can reasonably be expected to regard the probability and magnitude of possible harms implied by participation in the research to be no greater than those encountered by the subject in those aspects of his or her everyday life that relate to the research, then the research can be regarded as within the range of minimal risk."</p>	<p><b>Subpart D, § 46:</b> Recognizes four categories of research with children:          (1) Research not involving greater than minimal risk;          2) Research involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects;          (3) Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder/condition;          (4) Research not otherwise approvable that presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children.  <b>Definition of minimal risk, §46.102:</b>          Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.</p>	<p><b>Degree of risk</b><sup>122</sup>          "... research of <b>minimal risk</b> would not result in more than a very slight and temporary negative impact on the health of the person concerned" (p. 15)          E.g. obtaining biological samples without invasive intervention, such as saliva or urine collection  <b>"Low risk</b> describes procedures that might cause no more than brief pain or tenderness, small bruises or scars, or very slight, temporary distress: eg, a blood test"  <b>High risk</b> procedures (e.g. lung biopsy, arterial puncture, cardiac catheterization) in children "are not justified for research purposes alone"</p>	<p><b>2.1.6.</b> Research is <b>'low risk'</b> where the only foreseeable risk is one of discomfort. Where the risk, even if unlikely, is more serious than discomfort, the research is not low risk.  <b>2.1.7.</b> Research is <b>'negligible'</b> risk where there is no foreseeable risk of harm or discomfort, and any foreseeable risk is no more than inconvenience. Where the risk, even if unlikely, is more than inconvenience, the research is not negligible risk.</p>
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122 Note: These categories are adapted from Royal College of Pediatrics and Child Health, Ethics Advisory Committee, "Guidelines for the Ethical Conduct of Medical Research Involving Children" (2000) 82:2 Archives of Disease in Childhood 177.

**Table 2: Select Ethics Guidelines Regarding Minors' Participation in Research cont.**

	<p><b>CANADA</b>                      Tri-Council Policy Statement                      – Ethical Conduct for Research                      Involving Humans (amended to                      2005)</p>	<p><b>UNITED STATES</b>                      Code of Federal Regulations</p>	<p><b>UNITED KINGDOM</b>                      Medical Research Council                      Ethics Guide - Medical Research                      Involving Children (2004)</p>	<p><b>AUSTRALIA</b>                      National Health and Medical                      Research Council, National                      Statement on Ethical Conduct                      in Research Involving Humans                      (2007)</p>
<p><b>Consent,                      Assent &amp;                      Dissent</b></p>	<p><b>Art. 2.5:</b> Subject to applicable legal requirements, individuals who are not legally competent shall only be asked to become research subjects when:                      (a) The research question can only be addressed using individuals within the identified group(s); and                      (b) Free and informed consent will be sought from their authorized representative(s); and                      (c) The research does not expose them to more than minimal risk without the potential for direct benefits to them.  <b>Art. 2.6(d):</b> When a subject who was entered into a research project through third-party authorization becomes competent during the project, his or her informed consent shall be sought as a condition of continuing participation.</p>	<p><b>§46.408:</b>                      Permission of parent or guardian required for child to participate in research. Assent must be sought from children who are capable of assenting. IRB may waive parent/guardian permission where it "is not a reasonable requirement to protect the subjects" [This provision can be applied to authorize waiver of parent/guardian consent for mature minors in some circumstances.<sup>123</sup>]  <b>§46.402:</b>  <b>Assent</b> means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.</p>	<p>England, Wales and Northern Ireland: Common law applies to participation of minors in research, except for research subject to the Clinical Trials Regulations. Age of majority is 18, but minors aged 16 to 18 are presumed to be capable of giving consent. The Gillick case applies the mature minor concept in the medical treatment context. "In the absence of case law dealing specifically with research, the Gillick principles might reasonably be applied [to research], although the threshold for understanding will vary according to the complexity of the research. However there is continuing uncertainty about the application of these principles in research...." (p.23-24)</p>	<p><b>4.2.7:</b> [Subject to stated exceptions] ... specific consent to a child's or young person's participation in each research project should be obtained from:                      (a) the child or young person whenever he or she has the capacity to make this decision; and                      (b) [one or both parents, or other authorized representative].  <b>4.2.8:</b> An ethical review body may approve research to which only the young person consents if it is satisfied that he or she is mature enough to understand and consent, and not vulnerable through immaturity in ways that would warrant additional consent from a parent or guardian.  <b>4.2.9:</b> A review body may also approve research to which only the young person consents if it is satisfied that:</p>



<p><b>Art. 2.7:</b> Where free and informed consent has been obtained from an authorized third party, and in those circumstances where the legally incompetent individual understands the nature and consequences of the research, the researcher shall seek to ascertain the wishes of the individual concerning participation. The potential subject's <b>dissent</b> will preclude his or her participation.</p>	<p>Scotland: Age of Legal Capacity (Scotland) Act, 1991, c. 50: Age of majority is 18. Persons 16 to 18 are presumed to have capacity to consent, unless proven otherwise. Persons under 16 may give legally valid consent if a medical practitioner believes they are competent. "It is not entirely clear whether this Scottish statute covers consent to participate in research, but ... in the absence of [specific case law], the principles of Scottish law relating to consent to procedures and treatment might reasonably be applied." (p.24-25)</p> <p>For minors without competence to consent but who are able to assent "the investigator must obtain that assent in addition to the consent of the legally authorised representative."</p> <p>"If the child does not assent, this should be respected." (p. 26)</p>	<p>(a) he or she is mature enough to understand the relevant information and to give consent, although vulnerable because of relative immaturity in other respects;</p> <p>(b) the research involves no more than low risk;</p> <p>(c) the research aims to benefit the category of children or young people to which the participants belongs; <b>and</b> [either the young person is estranged from parent <b>or</b> it would be contrary to his/her interests to seek parental consent]</p> <p><b>4.2.14</b> A child or young person's refusal to participate in research should be respected wherever he or she has the <b>capacity to give consent</b> to that same research . . . . Where a child or young person <b>lacks this capacity</b>, his or her refusal may be <b>overridden</b> by the parents' judgement as to what is in the child's best interest.</p>
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123 For further discussion of when waiver of parent/guardian permission may be appropriate, see: Society for Adolescent Medicine, Guidelines for Adolescent Health Research (2003) 33 Journal of Adolescent Health 410-415.

