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BIOBANKS AND LONGITUDINAL STUDIES: WHERE ARE THE CHILDREN?

Julie Samuël[1], Nola M. Ries[2], David Malkin[3] and Bartha Maria Knoppers[4]

The inclusion of children in longitudinal research using biobanks raises specific ethical and legal issues. This article analyzes ethical frameworks concerning participation in biobanks and suggests that such frameworks, developed in the context of competent adults as research subjects, are not adapted for research involving children. It concludes that there is a need to elaborate guidelines specific to biobanks and longitudinal studies involving children and provides recommendations regarding parental authorization, the child's assent and consent, and on the return of results in this context.

The vulnerability of children has long raised ethical concerns about their inclusion in research, and past abuses in research has prompted their exclusion from subsequent study.[1] Over-protectionism has resulted in a lack of inclusion of children as research subjects, which has impeded the development of relevant medical therapies for them.[1] Furthermore, the extrapolation of data derived from adult-oriented studies for use with children has not always been appropriate. In response to this situation, international policies have begun to recognize the need to include children in research.[2] Recently, the European Commission reiterated the importance of including children by underscoring that children are not small adults and have specific needs.[3]

For more than sixty years, longitudinal studies have been used to observe the development of children, including factors that influence health and behaviours. The 1946 British National Survey of Health and Development was the first paediatric longitudinal study.[4,5] The goal was to study the cost of childbirth and the quality of associated health care.[5] Later, the 1958 National Child Development Study was created to investigate "social and obstetric factors linked to stillbirth and neonatal death".[6] The United States followed the example of the United Kingdom by launching two important longitudinal studies on children in the 1950s to study birth outcomes and health in surviving children: the National Collaborative Perinatal Project[7] and the California Child Health and Development Study.[8] These studies archived not only data but also the biological samples, such as serum, of the children involved.[4]

1. Lawyer and Project Manager, CRDP, University of Montreal
2. Research Associate, Health Law Institute, University of Alberta
3. Director, Cancer Genetics Program, Staff Oncologist, Division of Hematology/Oncology, Senior Scientist, Genetics & Genomic Biology Program, and Associate Chief of Research (Clinical), Research Institute The Hospital for Sick Children
4. Professor, Canada Research Chair in Law and Medicine

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Since 2000, longitudinal studies involving paediatric biobanks have been launched in several countries to study various aspects of children's health, as well gene-gene and gene-environment interactions.[9] The creation of large-scale "population" genomic biobanks[10] illustrates this recent phenomenon.[11] These involve the "study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems"[12] and health promotion. Some specifically involve children, including the Avon Longitudinal Study of Parents and Children,[13] the Canadian Healthy Infant Longitudinal Development (CHILD) Study,[14] the Copenhagen Prospective Study on Asthma in Childhood[15] and the US National Children Study,[9] for example.

The enrolment of children into longitudinal research studies raises unique ethical issues due to the potentially lengthy period of their involvement as research subjects. The data and samples collected may be stored and used throughout their lifetime. Thus, children grow up during the project, which means they will mature and develop the capacity to make independent decisions. This situation raises special concerns, not only due to the growing autonomy of the child and his/her place in the decision-making process, but also for the scope of parental authorization and degree of communication required with the parents and the child.

This editorial will focus on four specific issues in the context of paediatric biobanks: 1) parental authorization; 2) assent and consent of the child; 3) withdrawal from research; and 4) return of results. Each section begins with a review of international and Canadian policy documents on biobanks and on research involving children. This review is then followed by analysis and discussion of ethical questions raised by the four issues in focus. The HumGen International Database of Laws and Policies, Medline, PubMed and LexisNexis were used to identify the relevant policy documents and literature.

1. Parental authorization

International and Canadian policies on biobanking agree that the permission of the parents/legal representative is needed prior to collecting, storing and using the data and/or biological samples of their child. Parental authorization must be free and informed. To make an informed decision, policy statements require that researchers describe the purposes of the research, procedures, potential risks and benefits, the scope of the right to withdraw, potential re-contact, the types of data and/or samples to be collected, the means of storing the data and/or samples and security measures. Only a few policies on biobanking explicitly stress that the best interests of the child should be taken into consideration during the consent process, although this consideration may flow implicitly from the research ethics principle of respect for persons.[12,16] Indeed, parents/legal representatives are generally considered the best persons to determine what is best for their child.

Subject to applicable law, it may be possible to waive parental authorization under specific conditions, such as for epidemiological purposes or surveillance studies.[17,18] Yet, to ensure appropriate protection for children participating in research, such waiver of parental authorization is subject to approval by a research ethics board (REB).[12,19] Moreover, public health agencies generally have emergency powers to conduct research without parental authorization or an REB waiver if the research purposes are urgent and there is a need to protect and promote the health of children.

Information about the biobank initiative should be provided to parents in an understandable form and language.[20,21] Preferably, consent should be written.[12,18,19,20,21,22] It may also be oral or implied by voluntary actions.[12,19,21,22] Consent is a continuous process, which means that it should be sought again if there are significant changes in the research[12] and at predetermined intervals in long-term studies,[12] or for a new use of the data and/or samples collected previously.[18,20]

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It is interesting to note that none of the policy documents analyzed use terms such as “broad consent” or “open consent”, even though the ethical and legal aspects of broad consent have been well debated in the literature.[23,24,25] A broad consent is one wherein a participant agrees to the future unspecified uses of data and/or samples; in pediatric biobanks, the parent would agree on behalf of their child.[26] In longitudinal studies involving biobanks, the ethical acceptability of this type of consent is an important issue as specific details about all future uses of samples and information cannot be provided at the time of initial consent. Is it ethical to allow parents to provide a broad consent on behalf of their child?[27]

This question is much debated, with no consensus in policy documents and the literature. While some countries and international organizations have created normative documents that allow broad consent,[28] other countries require specific informed consent for all uses outside the original purposes of the biobank.[29] The latter position is based on the notion that the “more general the consent is, the less informed it becomes”.[30] Even if broad consent is an emerging practice in longitudinal research, there is still some resistance.[25,31] Some argue, however, that broad consent is the only form of consent that can be sought for a biobank that is meant to serve as a resource for various types of research questions into the future.[32] Parents may favour broad consent in some research contexts. For example, in a study involving childhood cancer tumour biobanking, most parents interviewed expressed a preference for broad consent to all uses of their child’s tissue rather than providing a new consent for each new project, provided appropriate ethics safeguards were in place.[33]

A problematic aspect of paediatric broad consent is that the initial permission is provided by the parents and not by the child.[26] When will the child – if ever – be able to exercise an autonomous choice with regard to the use of samples and data? Further, does the child have an opportunity to exercise the right to withdraw from the research?

A child’s capacity to express preferences about uses of data and samples increases as the child matures. As such, a child ought to have an opportunity to make choices about continued participation in research. In some jurisdictions the law recognises a “mature minor” doctrine, which states that a child who has the maturity to understand relevant information has the right to make an independent choice regarding matters such as health care and research participation.[34] This doctrine is consistent with research ethics principles that focus on the autonomy of research participants. Further explorations are needed to develop a model of informed consent that respects the rights of the maturing child within the context of paediatric biobanks. One approach may be to seek consent from the child when he/she reaches maturity.[26] This model poses minimal logistical difficulties if researchers follow up with the parent(s) and child on a regular basis. Researchers can plan to assess maturity and capacity to consent as the child enters adolescence. If researchers still have contact with the child when s/he reaches the legal age of majority, consent should be obtained from the individual for continued use of samples and data held in the biobank. If the anticipated period of contact with the family does not extend into the years when the child is gaining the maturity needed to make his/her own choices, or until the child reaches the legal age of majority, researchers will need an ethically and legally acceptable approach to continuing to use the child’s samples and data. This approach may involve seeking to re-contact the family or obtaining ethics approval that authorizes continued research based on the initial parental authorization, but waives a need to seek consent from the child.

2. Assent and consent of the child

International and Canadian policies are, for the most part, silent on the need to obtain the assent of the child before inclusion in biobanking research. Only the UNESCO, CIOMS and OECD guidelines expressly state that researchers should seek the assent of the child.[12,20,22] Various studies conclude that six or seven years is an appropriate age at which to first seek the assent of the child.[34] When seeking this

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assent, researchers need to consider the child's age, degree of emotional and psychological maturity, and intellectual capacities. Since children of the same age do not necessarily exhibit the same degree of emotional or intellectual maturity, the competency of the child to provide assent should be determined on a case-by-case basis.[35] For example, a child with a chronic medical condition may be more mature than a healthy child of the same age because of his/her experience with illness.[1] On the other hand, a child dealing with illness may be physically or emotionally unable to process complex decisions as effectively as when he/she was well. It may be impossible to obtain the assent of a child who is developmentally and cognitively challenged or, irrespective of age, intellectually immature.

The European Commission proposes three age categories to guide researchers in the assent process: 1) children from birth to age 3, where assent is impossible; 2) children from age 3 and up, where children from age 3 to 5 can understand some notions of altruism, and children from age 6 to adolescence have an emergent capacity to understand and express preferences; and finally 3) adolescents, who have an emerging capacity for making independent decisions in many areas of their lives.[3] Another category should be added, which is that of minors who are legally emancipated (i.e. by marriage or parenthood) or mature minors. Subject to applicable law, these minors may provide informed consent even if they are below the age of majority.[12] In Canada, however, the applicability of the mature minor doctrine in the context of research is still unclear since courts have yet to rule on this question.[34]

With regard to the information to be provided to the child when seeking assent, international and Canadian policies suggest elements such as: information about the project,[19,22,36] the right to decline to participate,[36] the right to withdraw,[36] and the potential risks and benefits of the research.[3,19,22] They do not provide more details on the elements to include in the assent discussion and documentation. Thus, it may be useful to refer to the elements of informed consent to ensure that the child receives all appropriate information.[3] These elements include the obligation that information be disclosed in an age appropriate language[22] and in accordance with the child's maturity and intelligence.[12]

No consensus exists on how assent should be documented. The European Commission and the International Conference on Harmonisation (ICH) recommend the use of age-appropriate information and documents to obtain the assent of the child.[3,36] International and Canadian policies do not necessarily require that an assent form be signed but provide that assent should be documented to prove that the rights of the child have been respected.[3] When the child is able to read and write, it is preferable to obtain his/her written assent.[3,37]

International norms and literature state that when a child reaches maturity or age of majority, consent for the continued use of data and/or samples collected in a longitudinal study should be provided.[12,19,38] As above, the ability to obtain informed consent may depend on the extent to which researchers maintain ongoing contact with participants and whether local law or research ethics approval permits a waiver of consent of a minor who reaches maturity or legal age of majority.

3. Withdrawal from research

If a child expresses a wish to withdraw from the biobank, issues may arise if there is disagreement between parent and child and where there is "informational entanglement"[39] (i.e. data or samples provide information on both the child and the parents, such as the case with placental tissue). If the child wants to withdraw or to continue to participate in the research against the will of the parent, the child's decision should be respected.[34,39] The parent's authorization on behalf of the child should no longer prevail when the child has capacity to make an independent choice.[39] In unusual cases of disputes regarding use of samples that contain entangled information, researchers should respect the choice of the party who seeks to withdraw.

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4. Return of Results

International and Canadian policies on biobanking provide some guidance on the return of results in research involving adults, which can be used to provide guidance on biobanks involving children. The majority of policy documents analyzed agree that general results about research should be disclosed to participants.[2,12,20,22,37,38,40] UNESCO's 2002 *Draft Report on the Collection. Treatment, Storage and Use of Genetic Data* underscores, however, that it may be difficult to follow this principle in large-scale epidemiological research projects where there are a large number of participants.[22] As for individual results, the OECD states that these should only be communicated to participants in exceptional cases, without providing more guidance on this point.[20] The majority of policies specific to genetic research stipulate that individual results, if and when they become available, should be communicated if: 1) they are clinically relevant for the health of participants;[12,16,22,38,40] 2) the data and samples allow the identification of the participants (i.e. they are stored in coded form);[16] and 3) participants want to know the results.[16,20,22,40,41,42]

Most policies analyzed recognize the importance of respecting participants' right to not know the results of research. One document proposes to extend this right to participants' relatives who may be implicated by the results of the research.[16] There is no consensus, however, on whether results should be disclosed to relatives against the will of the participant. The CIOMS recommends that results of genetic testing should not be disclosed to relatives without participant consent.[12,38] The WHO opens the door to such disclosure in its 2003 report, *Genetic Databases: Assessing the Benefits and the Impact on Human & Patient Rights*, and provides factors to consider before making a non-consensual disclosure: "(1) the availability of a cure or therapy; (2) the severity of the condition and likelihood of onset; (3) the nature of the genetic disease; (4) the genetic nature of the disease, i.e. – that it might have a significant implications for blood relatives; (5) the nature of any genetic testing that will be required; (6) the question of how the individual might be affected if subjected to unwarranted information, and whether the individual has expressed any views on receiving information of this kind".[43]

The return of results in the context of research involving children raises complex issues since typically results are communicated with the parent(s) and not directly with the minor participant. The disclosure of clinical test results to participants and their family members is a well-debated issue.[27,44] The same may not hold true with respect to research results. The emergence of a possible ethical duty to disclose research results to participants depends on several factors.[45,46] General research results should be communicated to participants throughout the research or at the completion of the research. Individual research results could also be communicated if they "meet the requirements of scientific validity, clinical significance, benefit (i.e. existence of prevention or treatment) and the absence of an explicit refusal to know".[45] At first, some longitudinal studies involving biobanks did not report individual results to participants, but were then confronted with important dilemmas because some of these results constituted "serious reversible threats to health".[34,47] For example, the Avon Study of Parents and Children revised its initial position not to return results by stating that "in cases of clinical testing where the abnormal findings would be immediately available […] the policy of non-disclosure should be abandoned and the parents given access to relevant information".[47]

How and to whom results should be communicated remain subjects of debate.[45] As for how results should be disclosed, a Canadian survey conducted specifically on the return of results to participants in the context of research involving children shows that good or neutral results may be communicated by letter or e-mail whereas bad results should be provided during a face-to-face visit.[46]

There is also no consensus on when to report general or individual research results.[27,44] Researchers must determine on an individual basis when it is appropriate to inform the child according to age, level of

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maturity and nature of the information to be reported. In this evaluation, researchers must take into consideration the right of the child to not know his/her results.[27,45]

Many questions remain regarding the return of results in paediatric research. For example, if researchers provide results to parents, do parents, in turn, have an obligation to disclose the results to their child? Should other members of the child's family also be informed of the results? Should the results be returned only to the child when he/she is mature? It would be important for researchers to elaborate a policy on the return of results to participants to specify which results will be disclosed, how, to whom and when. In addition, these elements should be discussed during the consent and assent process.

CONCLUSION

This analysis of the international and Canadian policies on biobanks focused on four complex issues related to the creation of paediatric biobanks: parental authorization, assent and consent of the child, withdrawal from research and return of results.

This analysis shows that there is a consensus regarding the requirement of parental authorization as well as unanimity on the elements to include in the informed consent process. In the context of biobanks, the use of broad consent raises specific concerns, particularly where children are concerned. While parents remain free to withdraw their consent at any time, in practice, a broad consent may deprive the child of his/her autonomy and right to withdraw from research. When there is an entanglement of information, the withdrawal of the child may also be problematic if the parent disagrees. In the absence of clear guidance, the literature concludes that the decision of the child should be respected. The policies analyzed do not provide much guidance on seeking the consent of mature minors or children who have reached the legal age of majority. Finally, the return of results in research involving children is complex and still under debate. There are no specific guidelines on how, to whom and when results should be communicated in the context of paediatric research.

As this analysis has demonstrated, current policies on biobanking in longitudinal studies are not yet appropriately adapted to paediatrics. Most of the policies reviewed only take into consideration the participation of competent adults and appear to exclude consideration of the interests of children. Therefore, we must extrapolate from these policies to elaborate guidelines that respect the rights of the child in the context of paediatric biobanks. The growing worldwide interest in creating such biobanks underscores a need to elaborate norms specific to this unique context. To this end, we recommend the following guidance:

1) It is important to involve children in research to understand better the factors that influence health and disease and to inform development of new and improved interventions and therapies;

2) It is equally important to ensure children are provided appropriate protections as participants in research and that their rights and interests are respected;

3) In seeking parental authorization to involve children in research, researchers should provide details about how (or if) the child's assent and/or consent will be sought in the future, how reporting of results will be handled, and how withdrawal will be managed, particularly in the event of future conflicts between the parent(s) and child;

4) Parental authorization must give way once the child is able to make their own decisions;

5) Children should have an opportunity to assent to continued participation in research when they develop the capacity to express preferences;

6) Children should have an opportunity to consent to continued participation in research when they develop the capacity to make informed, autonomous choices in regard to research participation (i.e. they attain mature minor status in this context)), if they

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become an emancipated minor, or when they reach the legal age of majority;

7) If researchers consider it is not feasible to seek assent and/or consent from minor participants (e.g. because researchers do not maintain ongoing contact with participants), they should seek ethics approval that authorizes continued research based on the initial parental authorization, but waives a need to seek assent or consent from the child;

8) Researchers should develop policies and procedures for handling research results and managing withdrawal decisions and communicate with participants about these matters during informed consent discussions.

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[1] Eric Kodish, *Ethics and Research With Children: A Case-Based Approach* (New York: Oxford University Press, 2005).

[2] World Medical Association, *Declaration of Helsinki*, Tokyo, 2004.

[3] European Commission, *Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population: Recommendations of the Ad Hoc Group for the Development of Implementing Guidelines for Directive 2001/20/EC Relating To Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use*, Brussels, 2008.

[4] P.J. Landrigan *et al*., "The National Children's Study: A 21-Year Prospective Study of 100 000 American Children" (2006) 118(5) *Pediatrics* 2173; M. Wadsworth, D. Kuh, M. Richards & R. Hardy, "Cohort Profile: The 1946 National Birth Cohort (MRC National Survey of Health and Development" (2006) 35 *International Journal of Epidemiology* 49.

[5] Medical Research Council, "Brief History of the National Survey of Health and Development" online: http://www.nshd.mrc.ac.uk/history/history.htm (last visited 9 October 2008).

[6] C. Power & J. Elliott, "Cohort Profile: 1958 British Birth Cohort (National Child Development Study)" (2006) 35 *International Journal of Epidemiology* 34.

[7] The National Archives, "Electronic Records From NIH, Record Group 443, National Collaborative Perinatal Project, 1959-1974" online: http://www.archives.gov/research/electronic-records/nih.html (last visited 9 October 2008).

[8] As cited in B.J. Van den Berg, R.E. Christianson & F.W. Oechsli, "The California Child Health and Development Studies of the School of Public Health, University of California at Berkley" (1988) 2 *Paediatric and Perinatal Epidemiology* 265.

[9] See e.g. The National Children's Study, online: http://www.nationalchildrensstudy.gov/Pages/default.aspx (last visited 9 October 2008); Danish National Birth Cohort, online: http://www.cls.ioe.ac.uk/text.asp?section=00010001000500090002 (last visited 9 October 2008); All Babies in South-East Sweden (ABIS), online: http://www.abis-studien.se/ (last visited 9 October 2008); The Norwegian Mother and Child Cohort Study (MoBa), online: http://www.fhi.no/eway/default.aspx?pid=238&trg=MainArea_5811&MainArea_5811=5903:0:15,3046:1:0:0:::0:0 (last visited 9 October 2008).

[10] "A population biobank is a collection of biological materials that has the following characteristics: i) the collection has a population basis; ii) it is established, or has been converted, to supply biological materials or data derived therefrom for multiple future research projects; iii) it contains biological materials and associated personal data, which may include or be linked to genealogical, medical and lifestyle data and which may be regularly updated; [and] iv) it receives and supplies materials in an organised manner". Council of Europe, *Recommendation Rec(2006)4 of the Committee of Ministers To Member States on Research on Biological Materials of Human Origin*, Strasbourg, 2006, art. 17, online: https://wcd.coe.int/ViewDoc.jsp?id=977859 (last visited 9 October 2008).

[11] See e.g. P3G, online: http://www.p3gconsortium.org (last visited 9 October 2008).

[12] Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Epidemiological Studies*, Geneva, 2008, online: http://www.cioms.ch/080221feb_2008.pdf (last visited 9 October 2008).

[13] Avon Longitudinal Study of Parents and Children, online: http://www.bristol.ac.uk/alspac (last visited 9 October 2008).

[14] Canadian Healthy Infant Longitudinal Development (CHILD) Study, online: http://www.allergen-nce.ca/Research/Network-Wide_Research/Canadian_Healthy_Infant_Longitudinal_Development_(CHILD)_Study_.html (last visited 9 October 2008).

[15] H. Bisgaard, "The Copenhagen Prospective Study on Asthma in Childhood (COPSAC): Design, Rationale, and Baseline Data From A Longitudinal Birth Cohort Study" (2004) 93(4) *Ann Allergy Asthma Immunol* 381.

[16] United Nations Educational, Scientific and Cultural Organization (UNESCO), *International Declaration on Human Genetic Data*, 2003, online: http://portal.unesco.org/en/ev.php-URL_ID=17720&URL_DO=DO_TOPIC&URL_SECTION=201.html (last visited 9 October 2008).

[17] Human Genome Organization (HUGO), *Statement on the Principled Conduct of Genetics Research*, (1995) 6 *Eurobios Journal of Asian and International Bioethics* 59.

[18] World Medical Association, *Declaration on Ethical Considerations Regarding Health Databases*, Washington, 2002.

[19] Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada

 ISSN 1718-9314

and Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*, Ottawa, 1998 (with 2000, 2002, 2005 amendments).

[20] Organization for Economic Co-operation and Development (OECD), *Draft Guidelines for Human Biobanks and Genetic Research Databases: Text for Comments*, 2008, online: http://www.oecd.org/document/12/0,3343,en_2649_34537_40302092_1_1_1_1,00.html (last visited 9 October 2008).

[21] Canadian Institutes of Health Research (CIHR), *CIHR Best Practices for Protecting Privacy in Health Research*, Ottawa, 2005.

[22] United Nations Educational, Scientific and Cultural Organization (UNESCO), *Draft Report on the Collection, Treatment, Storage and Use of Genetic Data*, Paris, 2002.

[23] J.E. Lunshop, *et al.*, "From Genetic Privacy To Open Consent" (2008) 9 *Nature Reviews Genetics* 406.

[24] E. Von Mutius, M. Kabesch & F. Kauffmann, "Trends in Ethical and Legal Frameworks for the Use of Human Biobanks" (2007) 30 *Eur Respir J* 373.

[25] B.M. Knoppers, "Biobanking: International Norms" (2005) 33:1 *Journal of Law, Medicine & Ethics* 7.

[26] W. Burke & D.S. Diekema, "Ethical Issues Arising From the Participation of Children in Genetic Research" (2006) 149 *Journal of Pediatrics* S34.

[27] L.F. Ross, "Ethical and Political Issues in Pediatric Genetics" (2008) 148C *Am. J. Med. Gen.* 1.

[28] *Human Tissue Act*, C. 30, 2004, London, online: http://www.opsi.gov.uk/acts/acts2004/ukpga_20040030_en_1 (last visited 9 October 2008); *Human Genes Research Act*, 2000, RT I 2000, 104, 685, Estonia, online: http://biochem118.stanford.edu/Papers/Genome%20Papers/Estonian%20Genome%20Res%20Act.pdf (last visited 9 October 2008); *Act on Biobanks No. 110/2000*, 2000, Reykjavik, online: http://eng.heilbrigdisraduneyti.is/laws-and-regulations/nr/31 (last visited 9 October 2008); German National Ethics Council, *Biobanks for Research*, 2004, Berlin, online: http://www.ethikrat.org/_english/publications/Opinion_Biobanks-for-research.pdf (last visited 9 October 2008); Human Genome Organization (HUGO), *Statement on DNA Sampling: Control and Access*, 1998, London, online: http://www.hugo-international.org/img/dna_1998.pdf (last visited 9 October 2008); World Health Organization (WHO), *Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services*, 1997, Switzerland, online: http://whqlibdoc.who.int/hq/1998/WHO_HGN_GL_ETH_98.1.pdf (last visited 9 October 2008); Ministry of Health, Labour and Welfare of Japan, *Ethical Guidelines for Analytical Research on the Human Genome/Genes*, 2001, Tokyo, online: http://www.eubios.info/EGHGR.htm (last visited 9 October 2008).

[29] See e.g. Italian Society of Human Genetics, *Guideline for Clinical Protocols of Genetic Research*, 2006; National Consultative Ethics Committee for Health and Life Sciences, *Ethical Issues Raised by Collections of Biological Material and Associated Information Data: "Biobanks", "Biolibraries"*, Opinion no 77, 2003, online: http://ec.europa.eu/research/biosociety/pdf/opinion_77.pdf (last visited 9 October 2008).

[30] V. Arnason, "Coding and Consent: Moral Challenges of the Database Project in Iceland" (2004) 18(1) *Bioethics* 27.

[31] A. Cambon-Thomsen, E. Rial-Sebbag & B.M. Knoppers, "Trends in Ethical and Legal Frameworks for the Use of Human Biobanks" (2007) 30 *Eur Respir J* 373.

[32] B.M. Knoppers, M.H. Abdul-Rahman & K. Bédard, "Genomic Databases and International Collaboration" (2007) 18 *KLJ* 291.

[33] M. Dixon-Woods *et al.*, "Human Tissue and 'the Public': The Case of Childhood Cancer Tumor Banking" (2008) 3 *BioSocieties* 57.

[34] N.M. Ries, "Growing Up As A Research Subject: Ethical and Legal Issues in Birth Cohort Studies Involving Genetic Research" (2007) 15 *Health Law Journal* 1.

[35] M.J. Field & R.E. Behrman, *Ethical Conduct of Clinical Research Involving Children* (Washington: The National Academies Press, 2005).

[36] International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceutical Human Use (ICH), *Guidance for Industry: Clinical Investigation of Medicinal Products in the Pediatric Population, ICH Topic E11*, implemented in Canada as of 2003.

[37] International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceutical Human Use (ICH), *Guideline for Good Clinical Practice, ICH Topic E6*, 1997 (with 2002 amendments).

[38] Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, Geneva, 2002.

[39] S. Holm, "Informed Consent and the Bio-banking of Material from Children" (2005) 1(1) *Genomics, Society and Policy* 16.

[40] Council of Europe, *Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research*, Strasbourg, 2005.

[41] United Nations Educational, Scientific and Cultural Organization (UNESCO), *Universal Declaration on the Human Genome and Human Rights*, Paris, 1997.

[42] Council of Europe, *Convention on Human Rights and Biomedicine*, Oviedo, 1997.

[43] World Health Organization (WHO), *Genetic Databases: Assessing the Benefits and the Impact on Human & Patient Rights*, Geneva, 2003.

[44] Y. Joly *et al.*, "Pharmacogenomics: Don't Forget the Children" (2008) 6(4) *Current Pharmacogenomics and Personalized Medicine* 77.

[45] B.M. Knoppers *et al.*, "The Emergence of An Ethical Duty To Disclose Genetic Research Results: International Perspectives" (2006) 14(11) *Eur J Hum Genet* 1170.

[46] C.V. Fernandez *et al.*, "The Return of Research Results to Participants: Pilot Questionnaire of Adolescents and Parents of Children with Cancer" (2007) 48 *Pediatr Blood Cancer* 441.

[47] S.M. Mumford, "Children of the 90s II: Challenges for the Ethics and Law Committee" (1999) 81 *Archives of Disease in Childhood* F228.

 ISSN 1718-9314