GSP online Genomics, Society and Policy
2005, Vol.1, No.1, pp.16-26.

Informed Consent and the Bio-banking of Material from Children

SØREN HOLM

Abstract

This paper considers the ethical issues raised by biobanking of material from children who are not mature enough to give ethically valid consent. The first part considers consent requirements for entry of such materials in the biobank, whereas the second part looks at the issues that arise when a competent child later wants to withdraw previously stored materials, and at the issues that arise when there is informational entanglement between information about a parent and information about a child. The paper argues for three main conclusions:

1. That it is in most cases acceptable for parents to give proxy consent to entry of material from their children into biobanks, even though this is not strictly speaking in the best interest of the child;
2. that a right to withdraw from the biobank is more important when material has been entered with proxy consent; and
3. that disputes about the withdrawal of entangled information, i.e. information that is both about a parent and a child, should be resolved in favour of the child.

Introduction

This paper will consider the ethical issues raised by biobanking of material from children who are not mature enough to give ethically valid consent (i.e. who are incompetent to consent)[1] [2]. The first part will consider consent requirements for entry of such materials in the biobank, whereas the second part will look at the issues that arise when a competent child later wants to withdraw previously stored materials.
The standard view in the research ethics literature and the international declarations is that children, like other incompetent persons, can only be included in research projects that 1) cannot be performed with competent persons as research subjects, 2) are in the best interest of the child (or only minimally against their interest), and 3) has been consented to by a relevant proxy decision-maker. It is further generally assumed that the children's' parents should be the proxy decision-makers.
This standard view is, for instance expressed in paragraphs 24-26 of the most recent revision of the Helsinki Declaration from the World Medical Association:

> "24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the

Genomics, Society and Policy, Vol.1 No.1 (2005) ISSN: 1746-5354

> population represented and this research cannot instead be performed on legally competent persons.
> 25. 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.
> 26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate."[3]

Very similar provisions can be found in the Council of Europe's Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine:

> "Article 17 –Protection of persons not able to consent to research
> 1. Research on a person without the capacity to consent as stipulated in Article 5 may be undertaken only if all the following conditions are met:
> i. the conditions laid down in Article 16,sub-paragraphs i to iv, are fulfilled;
> ii. the results of the research have the potential to produce real and direct benefit to his or her health;
> iii. research of comparable effectiveness can not be carried out on individuals capable of giving consent ;
> iv. the necessary authorization provided for under Article 6 has been given specifically and in writing; and
> v. the person concerned does not object .
> 2. Exceptionally and under the protective conditions prescribed by law, where the research does not have the potential to produce results that directly benefits the health of the person concerned, such research may be authorized subject to the conditions laid down in paragraph 1,sub-paragraphs i, iii, iv and v above, and to the following additional conditions:
> i. the research has the aim of contributing, through significant improvement in the scientific understanding of the individual's condition, disease or disorder, to the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons in the same age category or afflicted with the same disease or disorder or having the same condition;
> ii. the research entails only minimal risk and minimal burden for the individual concerned."[4]

The consensus is quite clear that the person who can give informed consent to become a research participant is the paradigm case and research on persons incapable of giving consent is an aberrant case that must be accommodated within the consent

Genomics, Society and Policy, Vol.1 No.1 (2005) ISSN: 1746-5354

paradigm, if it is at all to be allowed. The consensus has been developed in the context of clinical research, but has later been extended to all kinds of biomedical research[5].

This accommodation is achieved by seeking a "consent equivalent" and by restricting the types of research that persons incapable of consenting can participate in. The restriction on types of research can be justified in three partially different ways.

The first is based on the historical fact that vulnerable groups have often been used in ethically problematic research and that if the incompetent could be used as research participants in ordinary projects there is a risk that they would become an easy source of research material.

The second focuses on the intersection of interests between the person with a specific condition and the group of sufferers with that condition. The argument is that even if a person does not realize a personal benefit from the research, he is benefited indirectly through the benefits accruing to the group. However, this justification is problematic in many cases where group membership is not stable (e.g. where the group identifier is a phase and not a state sortal). One situation where the argument is of doubtful validity is where the membership of the group in question is temporary and where most persons who are part of the research will no longer be members of the group when the benefits materialize. This could for instance be the case for children if a disease only afflicts a particular age group, or where a condition is rapidly progressive, or where research projects are very drawn out in time. Another such situation is where the benefits are of a kind that can only be enjoyed by people who are not yet members the group. This could for instance be the case if the knowledge sought in a project is exclusively knowledge about how to prevent the occurrence of the condition.

The third possible justification is the pragmatic one embraced by those who would really like to ban all research on children, but who realize that unless we allow some kinds of research without informed consent into conditions where all sufferers are incompetent, very little progress will be made in the treatment of such conditions (the "golden ghetto" argument), but such research should be limited to those projects that cannot be performed in any other way in order to minimize the infringements caused by research without consent.

All three justifications of restricting research to problems shared by the group in question are problematic in various ways, primarily because it is much easier to provide an argument for a complete ban on research using incompetent research subjects if one proceeds within the consent paradigm, than it is to provide an argument for this particular way of restricting research.

Best interest

What kind of interests of a child is it allowable for a proxy decision-maker to take into account when considering the child's participation in research projects?

Genomics, Society and Policy, Vol.1 No.1 (2005) ISSN: 1746-5354

It is generally assumed that in order for research on children to be ethically justified a higher level of scrutiny by research ethics committees, and closer attention to the details of the proxy consent given by parents, guardians or others is necessary. Many justifications can be (and have been) given for this difference between research in children and research in competent adults, and some of these are quite plausible. It is, for instance, quite plausible that proxy decision makers may in certain contexts underestimate the negative effects of pain and discomfort on children, or that children sometimes may be an easily exploitable pool of research subjects.

One way to protect against these abuses or to resolve these problems is to require proxy decision makers to make their decisions according to the best interest of the child. Since much of biobank research has no direct benefits for the research participants themselves this would seem to indicate that the research cannot be in the best interest of the participants and that proxy decision makers therefore cannot legitimately permit or consent to participation on behalf of a child. The arguments against the legitimacy of entering children into research then usually claim that research offering no "direct benefit treats the child merely instrumentally, as a means to the ends of others. [6]

But in real life we do accept that parents[7] can make a whole range of decisions for their children. We like to maintain that these decisions should always be made in the best interest of the child, but in practice we allow parents to make decisions that are clearly not in the best interest of the child[8] For example parents make decisions to bring children up in polluted and dangerous cities, they expose them to danger as pillion passengers on bicycles in busy traffic, they deny them the protection of the triple vaccine for measles mumps and rubella on the most fragile of fears about its safety compared with the palpable dangers of contracting any of these childhood diseases, or they are weighing the interests of one child against the interests of other children in the family (e.g. when choosing where to go on holiday).

We may try to hide this practice by claiming that the decisions we allow are in the long term best interest of the child, or that they are in the best interest of the child as defined by the parents, but this is often just obfuscation. It is obvious that the interests of others are allowed to play a role, and in many cases the proxy decision maker is fully aware of this fact. Is this legitimate and can it be extended to the research context?

According to the seminal work of Buchanan and Brock the best interest principle should be understood in the following way:

> "The best interest principle states that a surrogate is to choose what will best serve the patient's interests, in other words, that which will maximally promote the patient's good. The qualifier "best" indicates two important factors: Some interests are more important than others in that they make a larger contribution to the patient's good, and a particular decision may advance some of the patient's interests while frustrating others. Thus, according to the best interest principle, the surrogate must try to determine the net benefits to the patient of

Genomics, Society and Policy, Vol.1 No.1 (2005) ISSN: 1746-5354

> each option, after assigning weights reflecting the relative importance of various interests affected when subtracting the "costs" from the "benefits" for each option."[9]

The main problem in applying this principle is in defining what counts as "the patient's good". The principle ostensibly prevents a parent from taking account of the good of others, for instance the good of other family members or the good of the parent him or herself. It therefore protects the child against the obvious danger of parents making decisions primarily based on their own interests.

But on closer inspection the principle does not actually specify how we are to identify the interests of the child.

Do children for instance have "moral interests", i.e. interests in being treated as moral agents who want to discharge their moral duties? I have, with John Harris, argued that this is indeed the case and that there is no reason to presume moral turpitude in our children[10]. It may be a fact that children are psychological egoists, but just like in adults this is no reason to organise society as if egocentric interests are the only ones that they really have. Current restrictions on the use of children as research participants are therefore, in our view, to tightly drawn.

Children, data and sample collection

Let us move to the more concrete question of data and/or sample collection from children for research projects that have no possibility of helping the cohort of children who are the research participants. Under what conditions will a broader conception of "best interest" allow such research?
We should perhaps first note that if the data collection is very burdensome or painful for the child this may in itself rule out participation. But even in cases where the data collection is not burdensome or painful issues concerning privacy, ownership, personal integrity and future possible harm, broadly conceived, still remain.

How important are these issues, is the mere fact that some research uses identifiable samples and therefore in some sense breaches privacy sufficient to show that it is not in the child's best interest? On a strict definition of best interest it clearly is, because even a minimal breach is still a breach, but there seems to be no good reason why a parent should not be allowed to authorise this minimal transgression of the best interest standard, when parents are allowed to authorise many other transgressions.

This may sound like opening the floodgates to misuse of children as research subjects, so it is important to say something more precise about under what conditions parents should be allowed to consent to research that is not in their child's strict best interest.

These conditions are probably best approached *via negativa* by identifying situations where parents should not be allowed to give consent. This class of situations will include instances where[11] 1) the parents' have strong interests in the research going ahead that are not shared with the child, 2) the breach of privacy is not only

Genomics, Society and Policy, Vol.1 No.1 (2005) ISSN: 1746-5354

"technical" (i.e. privacy is breached in relation to the researchers) but public (i.e. privacy is breached in relation to people in the child's personal sphere), 3) the breach of privacy is continuing over time or is irreversible[12], 4) the research is likely to generate findings that will impact negatively on the child, 5) the cumulative effect of participation in longitudinal research exceeds reasonable limits, for instance because of repeated testing or sample giving.

These situations fall into three categories, one concerned with the interests of the parents themselves, one with the size of the burden and the breach of best interest, and one with the irreversibility of decision-making. Whereas research ethics committees can deal with the two last issues in their general assessment of a given project, the first issue is often only detectable at the level of individual proxy decision-makers and it will therefore be the responsibility of the researchers to exclude children where parents are deciding from their own interests and not from a consideration of the interests of the child.

If we compare these restrictions with current biobank research projects we will see that it is in most cases justifiable for parents to give proxy consent for their children.

Withdrawing from the biobank

It is, however, worth looking in more detail at the question of possible future harm (clause 4. above), because biobank samples from children may be analysed at any time during their life time, and beyond. We are therefore debating possible personal harms from such analysis that may fall within the next 90-100 years, and posthumous harms that extend indefinitely. I have discussed the issues raised by research use of samples from the dead extensively in two already published papers[13], and will therefore here only look at the possible personal harms during the lifetime of the persons in question. These may be of two kinds:

- Harms directly created by the analysis of the person's sample in the biobank
- Harms created by attribution of certain negative or stigmatising characteristics to a group to which the person belongs as a result of biobank research

The first kind of harm occurs when information is created which negatively affects the person in question, e.g. information about genetic disorders, or about the person's genetic lineage.

The second kind of harm occurs when biobank research links some negative or stigmatising characteristic with a group to which the person belongs or identifies with by showing and making public that this characteristic is more prevalent in that group[14].

Whether or not these kinds of harms are likely to (or will) occur cannot usually be determined at the outset of a biobank project. Completely new analytical or statistical techniques may be developed that enables completely new and unforeseeable research questions to be pursued.

Genomics, Society and Policy, Vol.1 No.1 (2005) ISSN: 1746-5354

We may argue that this is not a problem in so far as the person in question is warned about this during the original consent process, and knowingly donates tissue anyway; and some[15] might even argue that it should be possible to give up your right to withdraw your sample and data from the biobank, if you are well informed and know what you are doing.

In the case of material from minors entered into the biobank with proxy consent, the situation is, however different. Like all proxy decisions, a decision to renounce withdrawability is a decision I make on behalf of someone else. As argued above there is nothing inherently wrong in making irreversible decisions for children that are not in their strict best interest, but there is something wrong about making a decision irreversible that could just as well be reversible at the point when the child reaches decisional competence. There can be no reason, apart from the convenience of the researchers, to renounce withdrawability completely at the proxy consent stage.

We know that children when they grow up often differ from their parents with regard to preferences and values, and we do therefore have good reasons not to close off decisions that do not need to be closed off. This is the main thrust of Joel Feinberg's well known "right to an open future" argument[16].

Allowing a full right of withdrawal to the competent child, whose materials have been entered into the biobank with proxy consent, is therefore more important than allowing a full right of withdrawal to adult donors to the biobank.

Some specific withdrawal issues when information is entangled

Some specific issues concerning withdrawal of consent, data and samples occur in cases where there is what we can call "informational entanglement" in relation to data and samples held in the biobank and relating ostensibly to two different persons. This is regularly the case for data in parent-child cohort studies and for samples in biobanks containing placental tissue.

The entanglement in the placental tissue case is biological as well as informational. Knowledge about the size and condition of the placenta at birth gives us information about both mother and child, and the placenta is itself an intricate mix of tissues derived from both the mother and the foetus[17]. What should be the effect if one of the parties involved in creating the placenta withdraw consent to its continued storage? As long as the child is still incompetent this will in most cases not raise any practical problems, since the mother will be the proxy for the child, and will presumably also withdraw on behalf of the child[18]. But what if the child is now competent and there is disagreement concerning withdrawal?[19]

Saying that each has a right to withdraw based on the normal considerations concerning self-determination, creates the problem that we could as well argue for a right to continue in biobank research based on the same considerations. We therefore have a conflict of two rights with the same underlying justification. The mother could

Genomics, Society and Policy, Vol.1 No.1 (2005) ISSN: 1746-5354

claim that she was the one who gave initial consent and that she therefore has a primary claim to decide what should happen, but this will not solve the problem in this case because she did not only consent for herself, but also as a proxy for her child. We could just as well argue that the now competent child should have decisional primacy because her or she was not directly involved in the initial decision and should be given a chance to "correct" the decision of the proxy decision-maker. None of these two arguments for giving priority to one of the conflicting parties is particularly strong, and we therefore need to look for another solution.

In the case of pure informational entanglement we could try to disentangle the information, for instance by deciding piece by piece, who the information primarily concerns, and allow the primarily concerned person to decide. This approach is, however, not without problems, because some pieces of information are essentially about several persons. It is a fact about me that my mother is a nurse, that she is Danish etc., as well as these things being facts about her. Even for pure informational entanglement we can therefore not avoid giving an answer to the question about how to resolve disagreements about withdrawal of entangled information.

Here it is worth noting that we have always allowed some kinds of informational entanglement in questionnaire studies and databases. It is, for instance, seen as unproblematic to ask about and register a partner's or spouse's age, occupation or even congenital disorders, without seeking the informed consent of that person.

It is clearly possible to mount an argument that this is problematic (at least slightly). From the fact that I have told you my private information, does not follow that I have given you permission to give this information to anyone who asks. Without there being a full and explicit confidentiality and disclosure agreement between us, there will still be an implicit agreement about what information you can divulge and to whom. These implicit rules concerning the passing on of information revolves partly around harm and embarrassment, but also involves "need to know" and "closeness" considerations. These implicit rules still hold *vis-à-vis* researchers who cannot presume a right to get second hand information, but in most cases the information asked for and stored is of a kind that I can legitimately disclose about my family members to outsiders.

I claimed above that the right to withdraw from and the right to continue in research have similar justifications, but could it not be argued that they do not have the same strength? In the clinical research context the right to withdraw is, as mentioned above absolute, but there is no generally recognised right to continue in research[20]. It is, however, again important to note the differences between biobank research and clinical research. The issue of disputed entangled information involves the rights of two research participants against each other, not primarily against the researchers, whereas the similar rights in the clinical context are rights the participant hold against the researchers.

I don't think that there is a principled way of resolving this conflict, except that we may take cognisance of the fact that in the case of entanglement between parent and

Genomics, Society and Policy, Vol.1 No.1 (2005) ISSN: 1746-5354

child there is an asymmetry in the way the entangled information has been entered into the database or biobank. Whereas the information about the parent is there with the person's own, personal consent, the information about the child is there only with proxy-consent. Based on this asymmetry we can argue that disputes over withdrawal of entangled information, that cannot be resolved in dialogue between parent and child, should be resolved in favour of the child. If the now mature child wants to withdraw his or her information the information should be withdrawn, and if they want their information to remain it should remain, whether or not it is entangled with information about their parents.

Conclusion

In this paper I have argued for 3 conclusions:

1. That it is in most cases acceptable for parents to give proxy consent to entry of material from their children into biobanks, even though this is not strictly speaking in the best interest of the child;
2. that a right to withdraw from the biobank is more important when material has been entered with proxy consent; and
3. that disputes about the withdrawal of entangled information, i.e. information that is both about a parent and a child, should be resolved in favour of the child.

As long as one keeps the significant differences between biobank research and clinical research in mind, none of these conclusions should be particularly controversial.

---

[1] I will omit discussion of exactly when children become ethically competent to consent, and just note that I think that this happens a long time before they become legally competent in most countries.

[2] In this paper I use arguments developed through many years of discussions with my colleague John Harris. I have worked so closely with John that it is sometimes difficult to know where my ideas end and his begin. I hope that I have not been guilty of excessive plagiarism. Some of the ideas have previously been discussed in the context of clinical research in: J. Harris and S. Holm. Should We Presume Moral Turpitude in Our Children – Small Children and Consent to Medical Research. Theoretical Medicine 2003; 24: 121-129.; in S. Holm. Autonomy, Authenticity, or Best Interest: Everyday Decision-Making and Persons with Dementia. Medicine, Health Care and Philosophy 2001; 4: 153-159.; and in S. Holm, 2004. Conducting Research in the Alzheimer Disease Population: Balancing Individual, Group, Family and Societal Interests. In Ethical Foundations of Palliative Care for Alzheimer Disease. R. Purtillo and H.A.M.J ten Have, eds. Baltimore. The Johns Hopkins University Press: 320-329.
My thinking on these issues has also been greatly stimulated by participation in a workshop arranged by Dr. Lisbeth Knudsen as part of a research network sponsored by the European Commission, DG-Research (EUROPEAN NETWORK ON CHILDREN'S SUSCEPTIBILITY AND EXPOSURE TO ENVIRONMENTAL GENOTOXICANTS (QLK4-CT-2002-02198))

[3] World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975,35th WMA General Assembly, Venice, Italy, October 1983, 41st WMA General Assembly, Hong Kong, September 1989, 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

[4] Council of Europe. 1997. Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine.

[5] It is of considerable interest that this very strong requirement for consent arose first in medical research and that it is not yet accepted in many other branches of research with humans. This might lead one to believe that something specific to medical research lies behind this strong emphasis on consent. That medical research often involves bodily intervention and often creates risk of physical harm are two obvious candidates for distinguishing specific features of medical research. These features are absent from much of biobanking research, or the bodily intervention is minimal and/or performed by the research subjects themselves (e.g. taking a mouth swab).

[6] See for example P. Ramsey. 1970. The Patient as Person. New Haven, CT. Yale University Press, 11-19.; P. Ramsey. Children as Research Subject: A Reply. Hastings Center Report 1977; 7: 40.; and P. Ramsey. The Enforcement of Morals: Non-Therapeutic Research on Children. Hastings Center Report 1976; 6: 24. In an interesting review of these issues Lainie Friedman Ross suggests that parents may, if there is minimal risk, enter children into research because their entitlement so to do is part of parental autonomy rights. (L.F. Ross.1998. Children, families and health care decision making. Oxford: Clarendon Press, Chapter 7).This claim will not be further discussed here.

[7] We will here focus on parents as proxy decision-makers but the arguments that follow are valid for most other kinds of proxy decision makers as well.

[8] This is, for instance, rather obvious in cases where there is more than one child, but limited resources and where maximising the interests of one child will negatively affect the interests of the other child.

[9] A.E. Buchanan and D.W. Brock. 1989. Deciding for others - The ethics of surrogate decision making. Cambridge: Cambridge University Press, 94.

[10] Holm & Harris, op.cit. note 3.

[11] This is probably not an exhaustive list and not all situations in the list are equally problematic.

[12] Strictly speaking every breach of privacy is irreversible except in situation where it is literally true that ”if I tell you this secret I will have to kill you afterwards”. In normal life information cannot be withdrawn, e.g. if I have told you that our mutual friend Bill is impotent, I cannot later retract that information, because there is no reliable technique by which you can erase the information from your memory.
But in biobank cases this does not hold, since stored information is stored in a fully erasable medium and is usually not remembered by any person because although it may have been entered onto the system by a person, this will have been just one of many sets of data entered.

[13] S. Holm and R. Bennett R. Genetic research on tissues stored in tissue banks. ISUMA:Canadian Journal of Policy Research 2001; 2: 106-112.
S. Holm. The Privacy of Tutankhamen – Utilising the Genetic Information in Stored Tissue Samples. Theoretical Medicine 2001; 22: 437-449.

[14] The following is a non-genetic example but illustrates the problem. If exam results after secondary school are correlated with first names it is found that there are reasonably strong relations between exam results and names. The top names of the list are, as could be expected girls’ names (we know that girls generally do better in school than girls), but more importantly in the present context is that there is a correlation between having a mis-spelt first name and having low exam grades. Thus having a name like “Jonahtan” is linked to having low grades. Although this can easily be explained through a concept like “social inheritance”, i.e. having parents who can’t spell is likely to influence your educational achievement, it is probably not a finding that most would think of in advance. Thus this research project has created a new stigmatising feature.

[15] Including myself in work in progress.

[16] J. Feinberg. 1992. Freedom & Fulfillment – Philosophical Essays. Princeton, NJ. Princeton University Press.

[17] Similar issues are potentially raised in research on, and storage of blood samples from pregnant women since we know that these regularly contain foetal cells in such quantities that attempts have been made to use the foetal cells from this source for prenatal diagnosis, see for instance L. Jackson. Fetal Cells and DNA in Maternal Blood. Prenatal Diagnosis 2003; 23: 837-846.

[18] We can of course imagine situations where the mother and father are estranged and the father has the parental rights, but I will leave aside direct discussion of these, presumably rare situations, since they are morally isomorphic to discussions involving disagreements between the mother and the competent child.

[19] Informational entanglement may also occur between siblings, monozygotic twins being the limiting case where there is complete entanglement of genetic information, but in this paper I will only discuss the parent-child cases.

[20] But there is a right to continue receiving effective experimental treatment after a research project has ended. See paragraph 30 of the Helsinki Declaration, op.cit., note 4.

Genomics, Society and Policy, Vol.1 No.1 (2005) ISSN: 1746-5354