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Biobanking in pediatrics: the human nonsubjects approach

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Abstract

Pediatric biobanks are an indispensable resource for the research that will be needed to bring advances in personalized medicine into pediatric medical care. Investigators developing pediatric biobanks have struggled with the ethical and legal challenges that arise in pediatric research. This article explores how one biobank model, the 'human nonsubjects models', is able to respond to such common challenges as the role of the parent and the child in agreeing to research participation, re-consent at the age of majority, data sharing and return of research results. Although this approach does not involve formal informed consent, it is well-suited to pediatric biobanking owing to its potential to reduce risk to children through a combination of advanced deidentification techniques and extensive oversight.

Keywords

biobanking; data sharing; genomic research; pediatric research; research regulation; responsible conduct of research; return of research results

Personalized medicine has received a great deal of attention in recent years for the promise it holds in enabling providers to use genomic information to predict adverse reactions to medications, customize health screenings and evaluations, and guide advice on lifestyle modifications. It is not yet clear how or when these advances in medical care may reach children, but it is unlikely that research in adults will be adequate. Research using tissues and clinical information about adults does possess a modest potential to improve pediatric care, since humans retain largely the same genetic code throughout their life and many adults will be able to recall their childhood medical history. However, diagnostic and therapeutic approaches in pediatrics have changed rapidly over recent years. As a result, patients who are now adults were evaluated and treated differently when they were children compared with children receiving care today. More importantly, though, the diseases that require the most urgent attention are those that cause death in children. These diseases can never be understood looking only at adults.

In order for the practice of personalized medicine to be applied to children, genomic research will need to be conducted in children. An economical and efficient approach to

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such research is to develop genomic biobanks using biological samples and health information collected from children.

While pediatric biobanking is likely to be valuable in this way, it is less obvious which approach to developing and operating a genomic biobank will work best in children. Models used for adult biobanking have been applied on a limited basis to pediatric biobanking. These models vary from one another in numerous ways, but one useful way to organize them is on the basis of the scope of the samples they seek to include and the level of interaction investigators have with potential participants. On the basis of these characteristics, biobanks can be organized into the following four groups: biobanks that actively collect disease-specific samples and information; biobanks that actively collect samples and information from all persons without regard to disease status; biobanks that passively collect disease-specific samples and information; and biobanks that passively collect samples and information from all persons without regard to disease status (Figure 1).

Each model has its own set of strengths and weaknesses. Each is suited to attain some scientific goals and not others, and each carries with it economic and operational considerations that may affect those scientific goals. The strengths and weaknesses of each model can also be assessed on the basis of ethical and regulatory considerations. While all biobanks must address issues such as consent, data sharing and return of research results, the response each biobank is able to provide to those issues is framed by the model that was adopted in its development.

In this article, I will explore in greater detail the ethical and regulatory dimensions of the fourth biobank model, in which samples are collected passively without regard to disease status. This model will be called the ‘human nonsubjects’ model, and will explore the basis for this conceptualization in relation to the USA's human research protections. I will argue that because of the set of responses this model generates to common ethical and regulatory challenges in pediatric research, it is particularly well-suited for application to pediatric biobanking.

Human nonsubjects biobanking

Even though the ethical principles that guide research involving humans have been organized in widely accepted consensus documents like the Declaration of Helsinki, the regulations that governments have adopted to regulate research may vary widely. In the USA for instance, federal research regulations divide research into two main categories: human subjects research and nonhuman subjects research. Human subjects research is the more heavily regulated of the two, with every study requiring approval by a research ethics board, or institutional review board (IRB). Regulations divide human subjects research into several categories on the basis of the risk that subjects are asked to assume through their participation in the proposed study; the higher the risk, the tighter the regulation and oversight (Figure 2). This regulatory schema is frequently called the Common Rule, since it is shared by a number of US government agencies.

Nonhuman subjects research refers to all investigation that does not involve the participation of human subjects. Biomedical research that fits into this category includes, for example, animal studies, bench research utilizing cell cultures or purified biomolecules and epidemiological research based on ‘off-the-shelf’ data. In short, any study that does not involve the interaction of a researcher with a human in order to collect samples or information, and does not utilize information that directly identifies specific humans, is considered nonhuman subjects research [1].

Although the Common Rule treats all types of nonhuman subjects research similarly, we have proposed that certain types of research in this category merit heightened scrutiny and oversight. In particular, we have proposed a conceptual category we call 'human nonsubjects research' [2]. This type of research involves deidentified information on humans with or without coded biological samples. The Office of Human Research Protections published guidance documents in 2004 and 2008 clarifying which types of research using coded samples fit into this nonhuman subjects category [3,4]. According to these publications, both type 3 and type 4 biobanks are considered nonhuman subjects research, since samples are collected passively and stored without personal identifiers. Neither these Office of Human Research Protections documents nor the Common Rule recognize a 'human nonsubjects' category of research. But we have proposed the idea in order to highlight the special consideration that must be given to information derived from humans, even if that information is used in research that does not fall within the scope of the Common Rule (Figure 2).

Since human nonsubjects research falls within the category of nonhuman subjects research, US human research protections allow for such research to be conducted without oversight from an IRB and without obtaining the formal informed consent of those persons whose samples or information are to be included. However, when human nonsubjects research is conducted on deidentified human information, it will become human subjects research if that information is routinely or intentionally connected to the identities of particular humans.

In this way, US human research protections exert indirect influence over this type of research. The reidentification of samples would shift the location of such a research project from the relatively unregulated nonhuman subjects category into the human subjects category. If this were to happen, such a study would no longer be compliant with research regulations.

The regulations indirectly create the need then for biorepositories based on this model in order to develop robust methods to protect against reidentification. Vanderbilt University's (TN, USA) biorepository named BioVU is one of the few human nonsubjects biobanks in operation. Because of the novelty of this model, its development required the design of new deidentification tools and new policies to protect against reidentification [5]. In early 2010, this resource was expanded to include samples from pediatric patients. This expansion has required close consideration of how this resource, which utilizes the fourth biobank model, should respond to the ethical and regulatory considerations that are unique to pediatric research. These issues include parental consent and child assent, reconsent at the age of majority, data sharing and the return of research results.

Parental consent & child assent

Consent is both an ethical and a legal concept. Legal guidelines for consent usually restrict children under a certain age from consenting to their own participation in research, although the age at which they may assume this role varies internationally. However, these legal guidelines are based on the ethical concept that some children are not yet mature enough to make autonomous decisions to assume the risk involved in research, and this maturity does not necessarily correlate with age. When children are not able to provide their consent, either because they are not yet old enough or not yet mature enough, parents are usually recognized as having the authority to provide this consent. Once parents give their consent, children are often asked whether they would like to participate, since their willing participation is important for both the safety of the child and the successful conduct of research. When parents have the authority to consent to their child's participation, if the child agrees he or she is said to assent to participation.

Even though parents are usually considered to be the appropriate adults to consent to their children's participation in research, their authority to do so is not absolute. This is a significant difference between research in adults and research in children. Adults are generally free to give their consent to participate in research that is approved by the appropriate research ethics panel. Parents are similarly free to give their consent to their children's participation when the risks posed by the study are low. When the risks are higher, parental consent is balanced with extra protections [6]. The underlying ethical concept is that the autonomy of adults to agree to take on risk is extensive, but the autonomy of adults to agree for their child to take on risk is limited by the best interests of the child [6].

Not all research requires that investigators obtain the informed consent of potential participants. Biobanks based on the third or fourth biobank model, because they fall under the nonhuman subjects category, do not need to obtain informed consent before including biological samples or health information. A sample from an adult can be included without that person's consent, and a sample from a child can be included without his or her parent's consent. In this context, samples from children and samples from adults are treated the same.

There is no international consensus, however, on which types of research can be conducted without informed consent [7]. The investigators who developed BioVU solicited input from patients through a mail survey and focus groups and also consulted with the medical center's clinical ethics committee and legal counsel. As a result of the input they received, they decided to offer patients the opportunity to 'opt-out' from having their blood sample included in the biorepository [5,8]. More recently, a population-based survey we conducted in the Nashville (TN, USA) area demonstrated that support for a biobank that utilizes left over clinical samples and deidentified medical record information is 93.9% as long as patients are able to opt-out. When asked for their opinion about a hypothetical biobank which collects samples without asking for written permission, only 45.5% of respondents expressed support [Brothers KB, Morrison DR, Clayton EW, Unpublished data].

This survey was not specific to pediatric biobanking. In a separate study, we have explored parent support for extending BioVU to include children through semistructured interviews. In our discussions, parents were generally favorable to including children in BioVU. Many of them acknowledged the importance of conducting medical research to improve pediatric medical care, and liked that BioVU does not involve additional needle sticks. Most parents seemed to assume that they would have a choice about whether their child's information would be included, and gave their conditional support on being given this option. Even those parents who would allow their child's sample to be included wanted to be given the opportunity to choose [Brothers KB, Clayton EW, Unpublished data]. Given the importance of both respect for persons inherent in any medical research project and the importance of building trust in research, choosing an opt-out model for human nonsubjects biobanking seems very important.

However, informed consent and the opportunity to opt-out are not equivalent. The most obvious difference is that research utilizing an informed consent process requires that participants make an affirmative act to agree to participate; research based on an opt-out assumes that participants agree to be included unless they act to opt-out.

The role of authority is another important difference. Informed consent involves the expression by the participant of his or her values. The participant values the research being conducted, and therefore, is willing to assume the risks that are entailed by being a human subject in a research study. In order for this agreement to be meaningful, the person giving permission must have an adequate understanding of the risks involved and must have the legal and moral authority to make such a decision. In the case of a competent adult, that

authority is held by the subject themselves. In the case of a child, that authority is usually held by the parent.

Authority plays a different role in research utilizing an opt-out. In this case, the risk involved in being included in the study must be very low and the research being conducted must be consistent with the values of most patients. If this is the case, the vast majority of patients will be willing to participate. Offering the opportunity to opt-out of the research is a way to express respect for the wishes of those people who do not want to be included, so the opt-out procedure should be easy for patients to complete. In the case of BioVU, a check box is included on standard clinic check-in forms (Figure 3).

No specific legal authority is required to opt a patient out of the biobank by checking this box. In fact, seeking to confirm the authority of a person wishing to opt a patient out would serve only to complicate the opt-out procedure for patients. When the patient is a child then any family member bringing the child for medical care is allowed to opt him/her out of the biobank. In fact, even the child themselves, whether 10 or 17 years old, is able to choose to exercise an opt-out.

These procedures to make opting-out easy for patients minimize the chances that a patient will be included in the biobank when he or she prefers to be excluded. The cost is that some patients will be excluded when the person with legal authority to make legal decisions for them would have allowed them to be included. This trade-off is acceptable because there is no significant risk to a patient when he or she is opted out, and the scientific goals of a biobank should be attainable even if some patients are not included.

These procedures are particularly favorable in pediatric biobanking because they introduce flexibility for mature children. An opt-out model does not entail the same consent/assent distinction that is so important in research based on an informed consent. Instead, either parent or child may choose to exercise an opt-out. In this way, mature children are able to have a say in their research participation regardless of age at the same time that parents are able to protect their children from inclusion in a research resource to which they object.

Another corollary of the opt-out model is the need for oversight. Because the opt-out approach does not involve the robust exchange of information present in formal informed consent, investigators cannot assume that those patients whose samples have been included in the biobank are aware of the scope of the research being carried out. This is true even if the biobank has made efforts to notify the public of the studies being performed using the resource. Because the information included is health information, and samples are collected in the clinical setting, it is reasonable to assume that patients expect samples will be used for research to improve health and medical care. Also, since their choice not to opt-out is clearly an act of trust, investigators have a duty to carefully utilize samples for research that meets these patient expectations. To put it more simply, research on topics that are controversial or have social implications beyond improving health and healthcare is best performed using samples from individuals who explicitly approve of this use of their samples.

BioVU has chosen to implement a review process for all studies that will utilize samples. This process includes, among other elements, an ethics review intended to ensure that research being performed is targeted at equitably improving the health of patients, does not have controversial or discriminatory social implications and does not stigmatize specific groups. Patients who choose not to opt-out trust that their samples will be put to positive use; oversight of the resource attempts to ensure that this trust is well-placed. In order to further build trust, BioVU has plans to develop mechanisms to inform patients and the public about the types of research that are being performed using the resource.

Reconsent at the age of majority

Since biobanks are likely to retain biological samples for use in research over a long period of time, it is inevitable that samples collected from children will remain in use at the time those children reach adult age. This creates problems for research based on informed consent, since the person who originally consented to the child's participation (the parent) is no longer the person who has the authority to approve of continued research on that sample (the child who is now a young adult). For this reason, some have argued that investigators managing pediatric biobanks need to recontact subjects when they reach adult age [9]. This question has been not only a matter of ethical and legal debate, but also a significant logistical challenge for pediatric biobanks.

The human nonsubjects model frames this problem in slightly different terms. In this model, inclusion or exclusion from the biobank does not depend primarily on the authority of the person given the opportunity to opt a child out. Rather, the preference is to keep the opt-out procedure as convenient as possible. In this model, the transition of a person from child to adult does not change past approvals or disapprovals in the same way that this transition did for research based on informed consent. Children may express disapproval of their own participation in a biobank before or after they reach the age of majority.

For human nonsubjects biobanks, a novel problem therefore arises. The question of importance is no longer whether a young adult must be presented with an opportunity to opt-out, but rather whether a young adult can choose to be included in a human nonsubjects biobank as an adult when he or she was previously opted-out as a child. In the development of BioVU, an early decision was made to treat any choice to opt-out as a permanent decision. On the basis of the principle of respect for persons, it was concluded that requiring patients wishing to opt-out to check the appropriate box at every clinic visit would place an inappropriate burden on patients [10]. Thus, the policy of this biobank is that a patient who chooses once to opt-out will remain opted out in perpetuity. No mechanism has been developed or needed to reverse a past opt-out decision.

The principle of respect for persons favors a policy that provides an opportunity for young adults to reverse past decisions made by parents. For those who have not previously been opted-out, every clinic visit is an opportunity to opt-out and thus to reverse past decisions. This approach is therefore consistent with the 'periodic reconsent' model that has been proposed for genetic research in children [9]. However, for those who have been previously opted-out, either by their parent or by themselves, there is no possibility for such a reversal. This policy is currently acceptable, since a young adult patient is not significantly harmed by not being included in the biobank. The only harm is that some young adults who are very interested in contributing to research may not have an opportunity to contribute in this particular context.

However, simply erasing past opt-out choices at the age of majority is not acceptable. This practice would make remaining opted-out difficult, and would thus increase the chances that a patient is included in the biobank against his or her wishes. There may be both justification and patient interest in developing a mechanism by which young adults can actively reverse past opt-out decisions, but such a procedure should require an affirmative act by the young adult.

Data sharing

In current practice, data sharing policies for biobanks are set either through consent procedures or through research ethics boards. If data sharing was anticipated in the

development of a biobank, permission to share data can be included on informed consent documents.

In the case of pediatric biobanks, if a parent has consented for his or her child's sample or data to be shared with other investigators, then data can usually be shared. If sharing was not anticipated, then subjects might not have been told that data could be shared during informed consent procedures. In this case, investigators wishing to share data will need to consult with their institution's research ethics board or IRB. The IRB may approve data sharing, or may require investigators to recontact subjects to update their informed consent specifically for data sharing. Similar procedures may be required to determine whether young adults need to be recontacted to get their permission for the continued sharing of data that was collected when they were children.

The authors of a recent paper in *Science* disagree with this interpretation, and instead propose that sharing of data collected from children is very different from data collected from adults. They argue that data from population-based pediatric biobanks should not be shared, even if parents give consent, until the pediatric subjects reach adulthood and can themselves provide explicit consent for sharing [11]. They argue, in brief, that sharing data introduces additional risk to subjects. This is because data that is stored within a biorepository is tightly controlled by the investigators who assumed responsibilities when they obtained informed consent from research subjects. The original investigators are required to protect the privacy of the subjects and to remove data from use if subjects later withdraw their consent. Although in theory this legal and ethical responsibility extends to investigators who receive shared data, the ability of the original researchers to protect subjects' privacy and remove data from use if needed are both compromised once data have been shared.

We found this policy proposal flawed for a number of reasons [12], but the authors' observation that the sharing of data introduces additional risks to subjects is well taken. When samples and medical information have already been collected in the development of a biobank, the risks that subjects face thereafter relate primarily to their privacy. Sharing data to other investigators increases the chances that this privacy might be compromised in some way. Gurwitz *et al.* argue that this additional risk creates a need to supplement parental judgment with extra protections [11]. While we disagree that the protections need to go so far as to halt all data sharing for years, taking measures to decrease the risks to privacy inherent in data sharing is important for all four types of biobank. Therefore more judicious measures could be taken without threatening the scientific value of biobanks.

In the case of biobanks based on models one and two, deidentification schema can be undertaken to provide collaborating researchers with the data they need to attain their scientific aims with little else. Deidentification can be used on consented datasets even when subjects have agreed to have identified data shared with others.

For biobanks based on models three and four, additional deidentification tools can be applied prior to sharing. A team at Vanderbilt has developed informatics tools that can be used to quantitatively assess the reidentification risk of research datasets. These tools can identify records that are likely to be identifiable when compared with publicly available datasets on the basis of uncommon combinations of data features, such as demographics and diagnosis codes [13,14]. Once such highly identifiable records are identified, sufficient information can be removed to minimize reidentification risk.

For all four types of biobank, the level of deidentification that is required will depend on at least three issues: the depth of information that will be shared, the number of investigators who might have access to the data, and the data-use agreement that will govern the sharing.

When datasets are to be shared with an individual investigator for a specific study, the depth of data can be restricted to the needed information and the data-use agreement can enforce this narrow use. In such circumstances, elaborate deidentification methods are probably not necessary. However, when data will be shared with a large databank that will itself be utilized by a number of investigators, tools that can quantify and reduce reidentification risk should be used. This is especially true if detailed information will be shared, since such detailed information is not only more easily identifiable but also more likely to contain information about persons that should not be revealed to others.

Return of research results

Investigators working with biobanks have expressed interest in providing individual research results to participants if such results might be helpful [15]. Likewise, participants have expressed interest in receiving them [16,17]. Although the dilemma of how and when to release such findings is not unique to biobanks, there are at least six issues that make the question of return of results particularly complex with respect to biobanks used for genomic research: the number of results are large, results are generated over time through multiple studies; the clinical applications of genomic information, particularly in the area of risk assessment, are in early stages of development and not yet well-incorporated into routine practice; research laboratories are not likely to meet the standards required for clinical laboratories; research subjects may experience genetic findings as having personal significance; and genetic findings may have implications for the subject's family.

These issues have been the focus of extensive debate within the literature. Even though no consensus has been reached on many of these issues, investigators utilizing biobanks are already faced with making decisions about whether to return their results. As has been the case with data sharing, the informed consent documents initially used in the development of biobanks have not always provided adequate guidance. Many informed consent documents have explicitly stated that no results will be returned [18]. However, if investigators identify results that they consider to have urgent clinical utility, they should consult with their research ethics board or IRB to discuss whether that provision should be overridden. Some have argued not only that highly actionable research results should be returned, but that there is a developing legal obligation to do so [19].

Despite this claim of a developing legal obligation, there are significant barriers to returning results when the research subject is a child. Several commentators have proposed that results should be returned if they meet proposed criteria for analytic validity, clinical validity, clinical utility and ethical, legal and social implications [20–22]. These criteria were borrowed from the discourse on clinical genetic testing [23]. It may be that other elements of the discourse on clinical genetic testing will help frame the return of genetic research results when the research subject is a child. For example, genetic testing in children to identify risk for an illness that does not develop until adulthood is controversial, since no medical harm will result from delaying testing until the child can decide about testing when he or she reaches adulthood [24]. Analogously, some genetic research results that do not have short-term significance should not be returned until the child reaches adult age and can consent to receive that information [9].

Although these connections between clinical testing and research results can be helpful in guiding the discussion, the distinctions to be drawn between the clinical and research contexts are significant. For this reason, a great deal of conceptual and empiric work will need to be invested in the development of detailed guidelines for the return of genetic research results to children and their families. Adding complexity to this issue, research

funding sources have generally not provided resources to support the return of genetic results, and the design of some biobanks makes the return of individual results very difficult.

Biobanks based on models three and four only store deidentified information. This is not the same as anonymized information, since a number of methods could be used to ‘break the code’, such as matching genetic or demographic information with identified records from other sources. However, human nonsubjects biobanks in the USA can only remain compliant with the Common Rule if samples and clinical information remain deidentified. As noted earlier, the routine or intentional reidentification of records would shift these biobanks out of the nonhuman subjects category into the human subjects category. Since these biobanks do not operate on the same procedures that are required within that category, routine reidentification would render such biobanks noncompliant with research regulations.

On the other hand, these types of biorepositories gather samples and information through routine clinical care. In this setting investigators may not have relationships with patients, but providers do. While providers have a limited responsibility to provide a therapeutic benefit to research subjects, this responsibility is central to the patient–provider relationship. In addition, in contrast to a context focused exclusively on research, providers may have both the resources and the relationships appropriate for the careful application of genetic test results. The responsibilities and resources of the clinician do not necessarily require that individual research results be returned to patients, but they do support the perspective that patients, even pediatric patients, whose samples have contributed to the research effort should be able to derive an individual benefit from that research.

Even though Vanderbilt's type-four biorepository is unable to both return individual results to patients and maintain its mission to generate beneficial medical knowledge, the biorepository has generated the experience and tools needed to support a parallel effort to implement clinical pharmacogenomic testing. This model is favorable in a number of ways. First, patients are able to discuss their perspectives on testing with providers they trust before the testing is actually performed. Second, testing can be performed to meet the needs of patients who can benefit from testing, rather than restricting testing to persons who happen to meet research selection criteria. Third, testing can be performed in CLIA-approved laboratories and returned to providers through well-validated clinical tools. Fourth, the issues of consent and assent pertinent to pediatric care can be worked out in detail by experienced pediatric providers.

Conclusion

Informed consent is considered the ‘gold standard’ in the ethical conduct of research involving humans [7]. This status is well-deserved, and the attention that has been given to both informing potential participants and obtaining their permission is well-invested. Given this history, it is not surprising that the development of biobanks that do not follow this approach would attract attention, and even disapproval. Many of the type 1 and type 2 biobanks elicit the informed consent of potential research subjects, but because the permission is often open-ended for future research, so-called ‘blanket consent’, some consider this approach a departure from the established informed consent standard [25].

Likewise, type 3 and type 4 biobanks are being developed using procedures without direct precedent in the literature on informed consent. My colleagues who developed BioVU have argued that this model remains consistent with the provisions of the Belmont Report, even if it does not utilize formal informed consent [10]. Others have been concerned that such an approach will be taken as a move to ‘escape existing regulations’ so that research can be conducted ‘without further surveillance’ [7]. This concern may seem particularly pertinent

to pediatric biobanking, since the legal and ethical considerations related to pediatric research and informed consent are especially complex.

As I have shown, though, the human nonsubjects model of biobanking neither circumvents regulations nor makes concerns about pediatric research obsolete. Rather, this model frames those perennial concerns in research involving children in a way that has required new approaches to data management and intense effort in the area of oversight. This model does not eliminate operational headaches; the headaches it creates are substantial, even though they are novel.

Future perspective

The potential benefits of human nonsubjects biobanks then are primarily economic and scientific. The process of confirming their scientific utility has already begun [26], and their economic efficiency will need to be confirmed over time. If these biobanks are able to collect samples rapidly while saving costs, they may help providers deliver on the promise of personalized medicine sooner.

If that promise is to be fully realized, however, children will need to be among the beneficiaries of the ‘era of personalized medicine’. The human nonsubjects biobank model will be an important tool to help achieve that goal. This model provides a framework for responding to the important legal and ethical issues that arise in pediatric research, and is thus well-suited to pediatric biobanking. This model allows pediatric patients and their parents control over how their information is used, while at the same time minimizing risk to patients through careful deidentification and oversight.

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Executive summary

- ‘Human nonsubjects research’ is a conceptual category introduced by the author to highlight the heightened scrutiny and oversight that is required in research that involves information derived from humans, even if the investigators do not have contact with those humans.
- Parents must give informed consent for the participation of children in research. The ‘opt-out’ approach approximates the ‘periodic reconsent’ model that allows parents to protect their children, while allowing maturing children to assume an increased role in decision-making.
- Deidentification techniques that allow for the quantification of risk should be used to guide sharing of pediatric biobank samples.
- The human nonsubjects biobanking model precludes returning research results to patients. A favorable alternative is the development of biobanks for research in parallel with programs to implement genomic and pharmacogenomic testing into clinical care.

Figure 1. Schema of common genomic biobank models

Figure 2. Categories of research in the US human research protections regulatory schema
We propose the further division of nonhuman subjects research into the subcategories 'human nonsubjects research' and 'other nonhuman subjects research'.

V. THE BENEFITS AND RISKS OF YOUR PARTICIPATION

As described above, you will be participating in a research study that may have benefits and risks. The purpose of this section is to help you understand the benefits and risks of participating in the study. You should read this section carefully and discuss it with your doctor and family members before deciding whether or not to participate in the study.

Benefits: The only benefit to you is that you will receive a copy of the research results. You will not receive any financial benefit from participating in the study.

Risks: There are no known risks to participating in the study. However, there is a small risk that you may experience a side effect from the research. If you experience a side effect, you should stop participating in the study and contact your doctor immediately.

Consent: You must give your consent to participate in the study. Your consent is required for you to be included in the study. You can give your consent at any time, and you can withdraw your consent at any time without penalty.

☐ I agree to participate in the study.

☐ I do not agree to participate in the study.

PLEASE SIGN AND DATE AT THE BOTTOM OF THIS PAGE.

Signature: _____ Date: _____

Figure 3. The opt-out form used in BioVU, Vanderbilt University Medical Center's (TN, USA) biorepository