The Ethical Use of Pediatric Biospecimens in Research

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SUMMARY OF AN NIH WORKSHOP

Office of Biorepositories and Biospecimen Research
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A. INTRODUCTION

This 1-day workshop, convened by the National Cancer Institute (NCI) Office of Biorepositories and Biospecimen Research (OBBR), addressed ethical issues involved in the storage and use of pediatric biospecimens in research (see agenda, attachment 1). Invited participants included ethicists; patient advocates; legal experts; administrators of pediatric biorepositories; clinicians; and representatives from the Government, including the National Institutes of Health (NIH), Food and Drug Administration (FDA), and Office for Human Research Protections (OHRP) officials.

The goals of this workshop were as follows:

- To identify general ethical concerns regarding use of pediatric biospecimens in future research and develop policies and protections to mitigate these concerns where possible;
- To determine whether genomic research on pediatric biospecimens requires additional protections for research participants;
- To develop recommendations for inclusion in future versions of the *NCI Best Practices for Biospecimen Resources* to address whether reassent and/or reconsent is necessary when biospecimens are collected from children; and
- To develop appropriate policies related to the use of pediatric biospecimens for a large national biorepository.

The morning session was devoted to presentations describing the challenges in research with pediatric biospecimens. The afternoon session consisted almost entirely of interactive discussion sessions designed to gain input from all participants. This document summarizes both the morning presentations and afternoon discussions.

B. WELCOME

Carolyn Compton, M.D., Ph.D., NCI OBBR Director, opened the workshop by explaining the NCI's interest and goals (see above) in developing guidance related to the use of pediatric biospecimens in research. She then explained that a biospecimen resource (more commonly known as a biorepository) is defined by the NCI as a collection of human specimens and associated data for research purposes. It is the physical entity where the collection is stored as well as all relevant processes and policies. Biospecimen resources with large quantities of high-quality, clinically annotated biospecimens are critical to accelerate the development of molecular-based diagnostics and therapeutics for personalized medicine and to improve patient care.

Biospecimen resources provide the biospecimens needed to identify novel targets for detection, diagnosis, prevention, and treatment of cancers. Biospecimens are used to elucidate the

molecular mechanisms of neoplasia and develop a molecular-based taxonomy of cancer. Finally, biospecimens are essential in the identification of biomarkers for susceptibility, screening, and recurrence and identification of biologic variations that determine drug efficacy and drug toxicity.

Among challenges facing NCI-supported biospecimen resources are the lack of common procedures, standards, and management principles; common definitions; common computerized access to information on specimens; and common approaches to ethical, legal, and policy issues. To begin to address these challenges, the NCI developed the *NCI Best Practices for Biospecimen Resources*, which aims to provide a baseline for operating standards on which to build as the state of the science evolves, unify policies and procedures for biospecimen resources supported by the NCI or used by NCI-supported investigators, and improve the quality of human specimens used in cancer research. The document includes recommendations for addressing ethical, legal, and policy issues around responsible custodianship; informed consent; privacy protection; access to data and specimens; and intellectual property and data sharing. However, the *NCI Best Practices* includes only one statement regarding the use of pediatric samples, recommendation C.2.2.10, as follows:

> Studies that use identifiable biospecimens and/or data from children that are obtained with parental or guardian permission should consider the need for obtaining informed consent when a child reaches the legal age to consent for a research study. Such reconsent issues may best be addressed by [institutional review boards] at the time the board reviews the initial protocol.

Clearly, more guidance is needed on this issue.

In closing, Dr. Compton explained that topics for group discussion would encompass four major areas of concern: (1) The role of the institutional review board (IRB), (2) research participant characteristics, (3) biorepository policies and procedures, and (4) the parental permission/assent process.

C. Ethical Reflections on the Use of Pediatric Biospecimens in Research

Robert Nelson, M.D., Ph.D., Pediatric Ethicist, Office of Pediatric Therapeutics, FDA, identified some of the ethical questions around biospecimen research: Are biospecimens personal property or a community resource? Are biospecimens a part of self-identity with religious and cultural connotations? Does the status of a biospecimen vary according to the body part from which it was derived; e.g., blood, tumor, heart? Sensationalist news stories about stealing cadaveric tissue and harvesting organs further feed public concerns about biospecimen research.

To address some of these concerns, Dr. Nelson offered possible solutions, such as providing a donor with choices during the informed consent process (1) to limit the use of biospecimens to protocol-specific objectives, (2) to limit the use of biospecimens to disease-specific objectives, (3) to permit unlimited use of biospecimens, or (4) to require consent for any future use of biospecimens. In addition, he proposed that independent oversight of biospecimen resources be required and that an atmosphere of trust be established through transparency. Dr. Nelson also

emphasized the importance of appreciating deeply felt cultural and religious values about the use of biospecimens and suggested that the individualistic approach of the current research ethics and regulatory framework may be insufficient.

Another source of ethical conflict in biospecimen research relates to obtaining consent for the use of pediatric specimens. Dr. Nelson proposed that, in an ethical sense, the parent functions as the trustee of the child's specimen. As a trustee, the parent cannot transfer ownership of the child's specimen; in other words, the specimen is "held in trust." However, parental permission ceases to be effective when the child reaches the age of majority[1]; therefore, no active consent or permission exists for the continued use of the specimen. One approach to addressing this challenge is to link the biospecimen with the child's date of birth (DOB) and develop a specimen use protocol. For instance, if the current date minus the DOB is less than 18 years, then parental permission is effective. If the current date minus the DOB is greater than or equal to 18 years, then informed consent is required from the now-adult source of the specimen. If informed consent cannot be obtained, then informed consent must be either waived or the specimen must be delinked from individually identifying data prior to inclusion in research.

Other issues that require further consideration are what to do with the specimen if the child dies before reaching the legal age of majority and whether to obtain the child's assent at appropriate life transitions; e.g., when the child becomes a teenager. Under the Federal regulations, parental permission and the age-appropriate assent of children capable of supplying their agreement or a waiver of consent are prerequisites to human subjects research (HSR). Once a subject reaches the legal age of majority, he or she must consent as an adult to any continuing participation in research, unless the requirement is waived by an IRB. These regulatory mandates are complicated in the biospecimen arena where investigators may seek to conduct research with a stored specimen originally obtained from a child who has now reached the legal age of adulthood. Once a pediatric research subject reaches the legal age of majority, the previously acquired parental permission and childhood assent are no longer valid for that individual's continued participation in research.

If the child dies before reaching the legal age of majority, continued research using his or her stored specimen would not violate Federal regulations because deceased persons and their tissue are not within the regulatory definition of "human subject." However, ethical concerns about respect for individual autonomy may arise regarding the use of stored specimens derived from a child who did not have the opportunity to consent as an adult or perhaps even to assent as a mature child. Moreover, while the assent of grown children is not legally equal to consent, when teens who are approaching adulthood agree to participate in research, the significance of that decision cannot be discounted. For that reason, assent must be viewed as an ongoing process that should be revisited and updated as children mature.

Questions and Comments

In response to an inquiry regarding the development of policy on the use of pediatric specimens in research, Dr. Nelson suggested that whether children want the opportunity to reconsent

[1] The age of majority refers to the age at which an individual is legally considered to be an adult. While the age of majority is 18 in most states, it does vary according to state law and the activity involved.

periodically is an important consideration. A focus group involving children would be helpful in determining what children want although Dr. Nelson said that, from his experience, children are happy to contribute to research and curious to know how their specimen will be used.

D. Regulatory Perspective on the Use of Pediatric Biospecimens in Research

Lisa Rooney, J.D., OHRP Division of Compliance Oversight, provided an overview of Department of Health and Human Services (HHS) regulations related to HSR, particularly as they pertain to pediatric specimens. She explained that HHS regulations apply to institutions only when the following criteria are met:

- The research is supported by HHS or covered by assurance;
- The activity involves research as defined by the Code of Federal Regulations (CFR) at 45 § 46;[2]
- Human subjects[3] are involved;
- The research is not exempt; and
- The institution is engaged in HSR.

The creation of a biorepository is considered research according to 45 CFR Part 46.[4] However, the creation of a biorepository would ***not*** be considered HSR if biorepository personnel do not intervene or interact with human subjects to collect the samples and if biorepository personnel or research team members cannot readily ascertain the identity of the individuals who contributed specimens.[5] In general, an institution is engaged in HSR when employees or agents of the institution obtain data about the subjects of the research through intervention or interaction with them, obtain identifiable private information[6] about the subjects, or obtain the subjects' informed consent.[7] Notably, an institution that solely releases identifiable private or coded information or biospecimens to others for research purposes is not itself engaged in HSR.

When creating a pediatric biorepository that involves interaction or intervention with human subjects or identifiable private information from living individuals, IRB approval must be sought using the general criteria for IRB approval of research under Subpart A of the regulations (45 CFR 46.111(a)) and the child-specific criteria described in Subpart D regarding additional

[2] Systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge (45 § 46.102(d)).
[3] A living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information (45 CFR § 46.102(f)).
[4] Code of Federal Regulations. Title 45—Public Welfare. Part 46: Protection of Human Subjects. Washington, DC: U.S. Department of Health and Human Resources; 2000.
[5] "Guidance on Research Involving Coded Private Information or Biological Specimens," Office of Human Research Protections, DHHS, Guidance Document, October 16, 2008. Available at: http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm. Accessed December 18, 2008.
[6] Includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record) (45 CFR § 46.102(f)).
[7] "Guidance on Engagement of Institutions in Human Subjects Research," Office of Human Research Protections, DHHS, Guidance Document, October 16, 2008. Available at: http://www.hhs.gov/ohrp/humansubjects/guidance/engage08.html. Accessed December 18, 2008.

protections for children involved as subjects in research. When collecting tissue samples from children for repository storage and future research use, Subpart D (45 CFR 46.408) requires parental or guardian permission and, for children deemed appropriately mature, child assent to include child samples in the repository. Once subjects mature, however, permission/assent requirements no longer apply, and the IRB overseeing the repository must ensure that informed consent is obtained for the now-adult subjects unless the IRB finds and documents that informed consent can be waived under the criteria contained at Subpart A of the regulations, 45 CFR 46.116(c) or (d).

When determining if the regulatory waiver criteria apply once the subject matures, the HHS OHRP human subjects regulations require consideration of whether the research involves more than minimal risk to subjects and whether the waiver will adversely affect the rights and welfare of subjects. Another criterion for a waiver is whether it would be "practicable" to perform the research if consent were required. For instance, if the inability to locate and contact a significant percentage of proposed subjects would render a study scientifically invalid, then the "impracticability" regulatory standard would be met. The HHS Secretary's Advisory Committee on Human Research Protections (SACHRP) has discussed the practicability requirement for informed consent in its recommendations to HHS.[8] An additional consideration, according to the SACHRP, is whether ethical concerns would be raised if consent were required. For example, is there an additional and unnecessary threat to privacy created by relinking data to identifiers in order to contact individuals to obtain their consent for further research? The regulations also require that, whenever appropriate, subjects be provided with additional pertinent information after they have participated in the study.

Ms. Rooney closed her presentation by providing a variety of scenarios that helped clarify for workshop members when and how HHS regulations apply to research using pediatric specimens.

Questions and Comments

A question arose regarding the use of biospecimens collected from deceased individuals, which would constitute a significant part of the donor pool for a national biorepository. Although not a regulatory requirement, Ms. Rooney suggested that institutions consider questions about the use of specimens from deceased individuals under the auspices of an oversight committee.

E. IRB Perspective on the Use of Pediatric Biospecimens in Research

Mark Schreiner, M.D., who chairs two committees for the protection of human subjects at The Children's Hospital of Philadelphia (CHOP), shared an IRB perspective on the use of pediatric biospecimens in research. He said that CHOP, like many institutions, is struggling with the myriad questions around biospecimen use, including questions about one-time consent for future use of biospecimens (versus specific consent) and legal considerations regarding ownership. These and other challenging questions facing IRBs are discussed further below.

[8] Tilden S. SACHRP letter to HHS Secretary [letter]. January 31, 2008. Available at: http://www.hhs.gov/ohrp/sachrp/sachrpletter013108.html. Accessed March 6, 2009.

One-Time Consent. Dr. Schreiner cited a review of 30 studies including more than 33,000 subjects that investigated subjects' willingness to provide one-time consent for future use of biospecimens.[9] The author found that most subjects (79 to 95 percent) were willing to provide one-time consent and allow IRBs to determine appropriate use of their samples. There is, nevertheless, a minority of individuals who are not in favor of one-time consent. Arguments against one-time consent emphasize the importance of protecting individuals' autonomy and maintaining public trust.

Recontact at Age of Majority. Once a research participant reaches the age of majority, if the definition of HSR continues to be met under 45 CFR 46, either investigators must seek legally valid informed consent or the IRB must waive the requirement for consent for the individual to continue participation. However, recontacting participants at the age of majority presents a variety of challenges. For instance, participants often relocate after graduation from high school, and in some instances, participants have been hospitalized for prolonged periods of time, further hindering attempts to recontact. This issue is also complicated because in Pennsylvania, for instance, minors may give consent in limited circumstances; e.g., for counseling, testing, and treatment for sexually transmitted diseases; mental health treatment; and pregnancy testing and prevention.

Requests for Withdrawal. What should happen to a specimen when a participant withdraws from a study is an area of considerable discussion. Some groups have suggested that identifiable samples should be destroyed if a participant, upon being contacted for reconsent, asks to withdraw from the study.[10] However, it is difficult to destroy all samples and sample byproducts, particularly after they have already been distributed and/or deidentified. To destroy computerized data, for instance, would require purging the data from databases and all backup tapes, including images and data from whole genome studies. Altered materials (e.g., cell lines, cultures) present a special case as well; they may be considered a "scientific work product" and thus are no longer the same as donated material. Furthermore, if an anonymized sample is already being used in research, there is no way to control its future uses. The FDA has developed recent guidance on withdrawal of consent for research studies, and OHRP is currently developing such guidance and has released a draft.[11,12]

IRB Oversight of Biospecimen Resources. In the face of these numerous challenging questions, Dr. Schreiner recommended that IRBs focus on two major areas: (1) Obtaining assurance that storing samples in a repository poses no more than minimal risk and (2) providing an honest and complete description of the biorepository in the informed consent document, as described in

[9] Wendler D. One-time general consent for research on biological samples. *BMJ.* 2006 Mar 4;332(7540):544-7.
[10] Clayton EW, et al. Informed consent for genetic research on stored tissue samples. *JAMA.* 1995 Dec 13;274(22):1786-92.
[11] "Guidance for Sponsors, Clinical Investigators, and IRBs: Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials," Food and Drug Administration, DHHS, October 2008. Available at: http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0576-gdl.pdf. Accessed March 6, 2009.
[12] "Draft Guidance on Important Considerations for When Participation of Human Subjects in Research is Discontinued," Office for Human Research Protections, DHHS, December 1, 2008. Available at: http://www.hhs.gov/ohrp/requests/com120108.html. Accessed March 6, 2009.

OHRP guidance.[13] Repository operating procedures and policies should include backup and disaster recovery processes, confidentiality protections, data and sample sharing policies, and IRB oversight. Informed consent should include clear, binary options for future research; a description of the nature of possible future uses of the specimen; the biorepository location(s); and the process for handling identifiable linkages, if any.

Current practice at the CHOP IRB is to recommend using binary choices for future use statements in informed consent and to permit one-time general consent. In addition, the CHOP IRB ensures that consent forms describe what will happen after requests for withdrawal and that requests to use identifiable specimens are consistent with the informed consent document.

Questions and Comments

The group discussed the issue of limiting the number of options in informed consent forms. All seemed to agree that, when possible, consent forms should be kept brief and clear and that research participants should not be overwhelmed with too many choices regarding how their specimens will be used. This approach also reduces the burden on the biorepository, which would otherwise be required to implement a complex system to ensure compliance with those choices.

The group also considered whether a biospecimen could truly be anonymized in this era of genomics. On this topic, workshop participants held differing opinions. Dr. Schreiner cited a recent study that showed that if a researcher has a highly dense genomic profile from an individual, bioinformatics techniques could be used to determine whether that individual participated in a study by analyzing only the pooled summary data.[14] Some research studies obtain certificates of confidentiality, and while some participants noted that such certificates can be challenged in the courts, one participant reported that they had been upheld in several court cases.

Last, there was discussion about the implications of collecting and storing biospecimens for clinical purposes that subsequently are selected as possible specimens for research use. Dr. Schreiner stated his opinion that current regulations may not adequately address the use of clinically derived samples if there is truly no research intent at the time of collection. Legal experts indicated that if the original interaction was for clinical care and the biospecimens are not identifiable, then subsequent use of such samples for research does not constitute HSR. Therefore, IRB approval would not be required.

F. PANEL DISCUSSION

Panel discussion focused on four topics: (1) Withdrawal of consent, (2) impracticability as related to reconsent, (3) reducing privacy risks to research participants, and (4) preserving the autonomy of research participants.

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[13] "Issues to Consider in the Research Use of Stored Data or Tissues," Office of Human Research Protections, DHHS, Guidance Document, November 7, 1997. Available at: http://www.hhs.gov/ohrp/humansubjects/guidance/reposit.htm. Accessed March 6, 2009.

[14] Homer N, Szelinger S, Redman M, et al. Resolving individuals contributing trace amounts of DNA to highly complex mixtures using high-density SNP genotyping microarrays. *PLoS Genet*. 2008 Aug 29;4(8):e1000167.

Withdrawal of Consent. The panel first discussed how to proceed when a research participant withdraws consent after his/her specimen is already at the biorepository. One workshop participant pointed out that while the biorepository may have a regulatory obligation to destroy or cease use of the specimen because there is no longer informed consent for continued storage of the specimen for future research use, products (such as cell lines) made from that specimen alter the original specimen and could be considered scientific work products not owned by the donor and, therefore, not subject to withdrawal according to *Moore* v. *Regents of the University of California*.[15] Another workshop participant pondered the implications of considering biospecimens property and provision of a specimen to a biorepository as a property transfer (rather than a donation). Whatever the approach, informed consent forms must indicate clearly and explicitly what will happen if a research participant withdraws consent.

Impracticability related to Reconsent. The group next considered how to determine when reconsent—particularly reconsent at the age of majority—is impracticable. Examples of when reconsent may be impracticable include when research involves particularly large numbers of research participants such that the research results and related data analysis would lack scientific validity if conclusions were based only on those who consented. It was also suggested that reconsent should be considered impracticable when it increases the risk to research participants. For instance, accessing the information necessary to recontact subjects (e.g., names, Social Security numbers, phone numbers) increases privacy risk. Reconsent at the age of majority may be impracticable because of major life changes (e.g., leaving home) that make tracking and recontact more difficult. For retrospective studies, a more liberal IRB likely will agree that reconsent at the age of majority is impracticable and will thus waive consent, as long as those studies pose only minimal risk. For another perspective on reconsent, the NCI was encouraged to contact the National Children's Study, which is collecting specimens from 100,000 children and following them from before birth until age 21.

Ensuring Minimal Risk Research. The panel emphasized that risk must be minimal for research to proceed with a waiver of consent. One way to minimize risk to research participants is through information technology (IT) protections. One such example is a CHOP study, involving genotyping 100,000 children over 5 years, that contracts with an honest broker not part of the research to maintain the study database. All medical records go through a two-step encryption process that provides an encrypted identification number, and every specimen is barcoded with that encrypted number. The system, which cost approximately $30 million, is not accessible through the Internet, and investigators have no access to the database or to the keys that decrypt the data. While this system provides significant research participant protections, the subsequent limits to data sharing must also be considered.

Preserving Autonomy. Panel discussion concluded with a brief conversation about respecting research participants' autonomy. Panelists considered the possibility of offending research participants, and even harming them emotionally, by returning to them at the age of majority for consent. For example, asking cancer survivors for consent to use tissue collected years ago may cause them to reexperience a very painful part of their life. Available research suggests that pediatric survivors of cancer and families of children with cancer are motivated to see others benefit from their experience. However, as one patient advocate pointed out, their experience

[15] *Moore* v. *Regents of the University of California*, 51 Cal. 3d 120; 271 Cal. Rptr. 146; 793 P.2d 479.

could be enhanced by making the informed consent process more transparent. All agreed that clear communication with patients is needed in order to build the trust and cooperative spirit necessary for the continued participation of patients in research.

G. WHAT DO RESEARCH PARTICIPANTS EXPECT FROM THE CONSENT PROCESS?

Carol Weil, J.D., OHRP Division of Compliance Oversight (on detail at the NCI OBBR), described the findings of five studies that attempted to determine what research participants expect from the informed consent process. The results of these studies are summarized below.

2007 Public Responsibility in Medicine and Research (PRIMR) Working Group Report.[16] A literature review by the PRIMR Human Tissue/Specimen Banking Working Group revealed that there is strong public interest in having tissue samples used in research but that research participants do not want repeated contact for consent for each future research use and do not want repeated consent for research involving a different disease than the one originally studied. The literature review also indicated that research participants are concerned about unwanted disclosures of genetic information to insurers or employers.

Wendler and Emanuel, Archives of Internal Medicine.[17]A telephone survey of 504 older Americans suggested that after individuals give consent for research use of tissue, including clinically obtained tissue, they do not require reconsent for additional research uses of that tissue. Also noteworthy is that 85 to 90 percent of respondents would not impose greater safeguards on future research use of their tissue to study a different disease. The example given in the survey was diabetes; notably, had a more stigmatizing disease such as schizophrenia been cited as the example, the response may have been different.

Stegmayr and Asplund, British Medical Journal.[18] In a population-based study of informed consent for genetic research on blood stored for more than a decade, the overwhelming response from research participants was that their samples could be used in future studies without reconsent. A workshop participant noted that this study was conducted in Sweden where medicine is socialized and the people perhaps are more focused on serving the common good. Consequently, the findings cited here may not apply in the United States.

Kaufman et al., American Journal of Medical Genetics Part C: Seminars in Medical Genetics.[19] This article described a community engagement pilot study using focus groups to identify ethical implications of including children in a large biobank for genetic epidemiologic research. Focus group participants raised several concerns: (1) That it may be unethical to subject children to study burdens, risks, and discomforts if they cannot understand the study goals or the long-term nature of participation and (2) that parental permission without seeking assent even from young

[16] Report of the Public Responsibility in Medicine and Research (PRIMR) Human Tissue/Specimen Banking Working Group Part II. Tool F: Patient Attitudes. Boston, MA: 2007.
[17] Wendler D, Emanuel E. The debate over research on stored biological samples: what do sources think? *Arch Intern Med*. 2002 Jul 8;162(13):1457-62.
[18] Stegmayr B, Asplund, K. Informed consent for genetic research on blood stored for more than a decade: a population based study. *BMJ*. 2002 Sept 21;325:634-635.
[19] Kaufman D, Geller G, Leroy L, et al. *Am J Med Genet C Semin Med Genet*. 2008 Feb 15;148C(1):31-39.

children could encourage coercion. There was no consensus on how or when children mature, but most focus group participants felt that a series of early assents; reassent at a more mature stage; and, finally, consent processes at the age of majority would need to be developed.

2008 OBBR Informal Survey. In a small informal survey of nine pediatric survivors of cancer and parents of pediatric patients with cancer, respondents were asked how they would feel about being recontacted at the age of 18 to request continued use of their specimens in research. Some felt recontact would be intrusive; others felt that recontact is a right. None of the respondents wanted to be informed every time their tissue was provided for a specific cancer research project. Instead, they asked that informed consent documents state, as specifically as possible, what could be done with their tissues.

The concerns raised in these studies emphasize the importance of the regulatory criteria under the HHS human subjects regulations that require that a waiver of consent does not adversely affect the rights and welfare of research participants. There also needs to be a balance struck between empowering adults with choice and avoiding the invasiveness of unwanted contact. In closing, Ms. Weil emphasized the need for additional studies of the attitudes of pediatric survivors of cancer about reconsent at the age of majority to further inform guidance on this topic.

Questions and Comments

Group discussion revealed the need for a glossary of terms to ensure that the research community shares a common definition of key words. Words that require clarification include, for example, "anonymized," "coded," "delinked," "assent," and "consent."

H. Practical Perspective on Pediatric Biobanking

Jay Bowen, M.S., Biopathology Center (BPC), Research Institute at Nationwide Children's Hospital, described the history and role of the BPC, which is an organization providing specimens or specimen management services to the Pediatric Division of the Cooperative Human Tissue Network (CHTN), Children's Oncology Group (COG), and Childhood Cancer Survivor Study (CCSS) as well as other nonpediatric groups.

CHTN. CHTN collects tissues prospectively, according to the investigator's protocol, and therefore is not technically a bank. Tissues are taken under the guidance of a pathologist to ensure that patient care is not compromised and are provided in a variety of forms; i.e., fresh, frozen, paraffin blocks, slides. Notably, tissues are not linked to clinical trials (except those collected on COG protocols). In addition to the tissue sample, CHTN provides investigators with a copy of the pathology report, with all identifying information removed.

COG. COG banks tissues from around the world, capturing up to 90 percent of all pediatric cancers in the United States and Canada. Investigators submit tissue requests electronically via the COG or BPC Web sites. Following initial review by the BPC, the application is sent to the Statistical and Data Center and to the appropriate COG Disease Groups. COG receives a high volume of specimens (over 65,000 in 2007) and, on average, provides 15,000 specimens to investigators annually. Furthermore, research using COG specimens has resulted in more than

600 publications since the bank was formed in 2000, and a substantial number of them had high impact factors (greater than 5).

CCSS. CCSS comprises research participants who were diagnosed with cancer between 1970 and 1986, who were less than 21 years old at diagnosis, and who survived for at least 5 years after treatment. The participants, who number over 13,000, complete an initial 24-page questionnaire and subsequent biannual questionnaires about cancer diagnosis, therapy received, and health and quality-of-life outcomes. CCSS has a number of working groups to address lingering health challenges, including a working group on secondary malignancies.

Mr. Bowen briefly described the flow of materials through the BPC and described some of the unique products and features of the center, including specimen procurement kits, insulated specimen shipping containers, a central receiving facility that processes 50 to 70 packages daily, a morphology core, virtual imaging capabilities, a bioinformatics core, and a reference laboratory and nucleic acid core.

In closing, Mr. Bowen shared data indicating the marked increase in survival rates among pediatric patients with cancer over the years as a result of clinical trials. He also pointed out a challenge in conducting research on pediatric cancers: Because the number of new cases of pediatric cancers each year is low relative to new cases of adult cancers (10,000 versus 1,437,180, respectively), the amount of pediatric biospecimens available is limited.

Questions and Comments

A workshop participant pointed out a troublesome gap in pediatric cancer research: Treatment trials such as COG generally follow patients for 5 years, and the CCSS picks up when the child reaches age 18. Therefore, little is known about what happens to survivors of childhood cancer between treatment and adulthood. In closing, Dr. Compton emphasized the importance of resolving the ethical, legal, and policy issues around use of pediatric biospecimens to advance the treatment of pediatric cancers.

I. PANEL DISCUSSION

Panel discussion focused on (1) when and how to seek initial consent from patients and (2) how to determine when activities involving biospecimens are considered HSR.

Delayed Consent. Patient advocates pointed out that patients are often approached for informed consent at a difficult time in their lives—almost immediately after being diagnosed with cancer—and recommended that consent be delayed until a time when the patient is less anxious and is in a better position to integrate and understand the information presented. They added that the research community is not serving patients well when consent is requested at a time when patients are most anxious and confused. One advocate suggested that requesting consent at a time of high stress "borders on being coercive." Patient advocates therefore agreed that a more appropriate approach is to collect biospecimens during surgery, when biological material is already being collected for diagnostic purposes, and approach patients afterwards for consent for research use. Others agreed that there is a benefit to delaying consent but added that IRB approval would still be required. Further clarification from OHRP would be needed to determine

whether a delayed consent model would require waiver of informed consent for the initial collection.

Two concerns were raised regarding delayed consent. First, there was concern that not enough tissue would be retained for diagnostic purposes. To this Dr. Compton responded that clinical use always trumps research use. Second, there was concern that specimens initially collected for clinical care would not be of sufficiently high quality. This is because diagnostic procedures do not currently require high-quality specimens whereas research requires biospecimens of exceptionally high quality.

Patient advocates emphasized that most patients are committed to research and would likely be in favor of a regulatory environment that enhances the ability to conduct research. In other words, regulations should not present such a burden that they become a barrier to research. All panelists seemed to agree that not only is it important to ensure protection of human subjects, but it also is important to ensure maximum utility of biospecimens to promote research that will enhance the ability to treat cancers.

Determining HSR. Workshop participants sought clarification regarding when activities involving biospecimens are considered HSR, presenting several scenarios. When an investigator receives specimens from the BPC, if the specimens are deidentified and not clinically annotated with any identifiable private information, the recipient investigator is not engaged in HSR. If the recipient investigator receives only coded medical data along with the biospecimens, the specimens and data are not collected specifically for the investigator, and if there are biorepository operating policies or a contractual agreement in place by which the repository is prohibited from releasing the key to the code and the investigator cannot receive the key to the code, then research use of the specimens and data by the recipient investigator would not be considered HSR in accordance with OHRP policy.[20] Under these circumstances, the repository is sometimes referred to as an "honest broker" that protects patient privacy by serving as a third party intermediary that collects, stores, and distributes specimens and data to researchers. Who makes the determination about whether research constitutes HSR varies depending on the institution although guidelines recommend that the study investigator not make this determination him/herself.

J. Interactive Discussion: Should Consent Be Sought at Age of Majority From Former Pediatric Biospecimen Donors?

Ms. Carol Weil moderated this interactive discussion about whether consent should be sought from former pediatric biospecimen donors at the age of majority. Discussion addressed issues around recontacting donors to obtain consent, including who should initiate the recontact, when it should be initiated, and how it could be facilitated. The group also discussed the role of biorepository oversight in ensuring ethical use of pediatric biospecimens.

[20] "Guidance on Research Involving Coded Private Information or Biological Specimens," Office of Human Research Protections, DHHS, Guidance Document, October 16, 2008. Available at: http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm. Accessed March 6, 2009.

Who Should Initiate Recontact? The group considered who should be responsible for recontacting donors at the age of majority to seek consent. One workshop participant suggested that the central biorepository initiate recontact because it has the appropriate identifiers. However, if the biorepository is one step removed from the donor, as in the case of a national biorepository, then the local institution that collected the biospecimen should initiate recontact. Participants emphasized that donors should be recontacted by an individual/institution with which they have an established relationship so that there is a basis for trust. If recontact is judged to be impracticable, then research on banked biospecimens cannot proceed without either securing a waiver of consent or anonymizing the data.

When Should Recontact Be Initiated? Next, the group considered when to seek reconsent. Some argued that it is not necessary to reconsent individuals until their specimens are needed to address a specific research question. Others argued that, as a general policy, reconsent should be sought at the age of majority. Proponents of the latter approach pointed out that the perceived logistical and informatics burdens of having to obtain reconsent could stall research efforts in the field of pediatrics. In addition, it may be more difficult to locate individuals to obtain consent later in their lives when they have fewer points of contact with the cancer research community. There were also concerns about the legality of holding biospecimens in reserve beyond the age of majority without explicit consent. A workshop participant responded that retaining a biospecimen in a repository without intent to use it constitutes minimal risk, so consent can be waived.

How Can Recontact Be Facilitated? The group agreed there are two significant challenges to recontacting donors at the age of majority to obtain consent: It is often impracticable, and it may be perceived as intrusive. To surmount these challenges, the group proposed that biorepositories that anticipate a need to recontact donors consider building ongoing relationships with research participants. A practical way to maintain contact with research participants and one that allows the participant to be in charge of the interaction is to create a central Web site that keeps participants abreast of developments related to research. The site could report research results in aggregate and invite research participants to sign up for listservs. It could also offer an option to "self-report" on health status and/or to offer consent via an online mechanism.

Workshop participants shared two concerns about self-reporting as a mechanism for maintaining contact with research participants. First, they were concerned about the quality of self-reported information. In response, Dr. Compton pointed out that quality control issues arise even when medical doctors report data. Furthermore, some argue that the research participant—as the source—is in fact most likely to provide accurate data. A workshop participant added that CCSS offers research participants the option to participate in genome research by completing an online questionnaire. These self-report data are then verified with followup calls. Workshop participants also were concerned that there would be bias in self-reporting because only the most motivated individuals would participate. It was suggested that this be addressed through outreach and education efforts that encourage people to be involved.

Other approaches suggested by workshop participants for maintaining contact with research participants included the following:

- Disseminating informational materials such as brochures and newsletters to oncology waiting rooms, patient advocacy groups, and other appropriate venues; and
- Assigning individuals within the biorepository as patient advocates whose primary responsibility is to keep in touch with research participants.

While none of these approaches completely circumvents the challenges associated with recontacting individuals for reconsent at the age of majority, they nevertheless set the stage for recontact by maintaining a connection with research participants.

Biorepository Oversight. In closing, the group discussed the role of biorepository oversight in ensuring ethical use of pediatric biospecimens. One workshop participant emphasized that the principal investigator should not determine whether his/her research study presents minimal risk to research subjects as this is a key responsibility of the IRB. Another participant pointed out that many biorepositories currently have tissue utilization committees that ensure proposed research uses of biospecimens are consistent with the original informed consent document. Overall, workshop participants agreed that transparency about biorepository oversight is essential to ensuring public trust.

The subject of trust also arose in the context of ethnic and minority populations. While the literature suggests that many donors prefer not to be reconsented in part because of an underlying trust for physicians and researchers, there are nevertheless minority groups, such as Alaska Natives, African Americans, and Native Americans, who may not have the same confidence in the biomedical research enterprise and therefore may be uncomfortable with an IRB waiving reconsent.

To reduce privacy risks to research participants, one workshop participant suggested that all data be delinked, but Dr. Compton argued that delinking data is not an option for a biorepository of the highest quality. She explained that it is valuable to maintain contact with research participants to continue to enrich the data through followup. An alternative approach to maintaining patient identifiers would be to establish a one-way coding system to allow followup data to flow from patient medical records to the biospecimen resource.

K. Interactive Discussion: Does Genetic Research Present Additional Considerations for the Use of Pediatric Biospecimens?

Elizabeth Thomson, D.N.Sc., R.N., National Human Genome Research Institute, introduced this interactive discussion by presenting NIH guidelines indicating that children (defined by the NIH as individuals under the age of 21) must be included in research unless there are scientific or ethical reasons not to do so. Under 45 CFR 46 Subpart D, additional protections are required for children involved in research; e.g., obtaining parental permission and child's assent when appropriate. In addition, Subpart D describes four types of research:

- Research not involving greater than minimal risk;
- Research involving greater than minimal risk but with direct benefits to the child expected;
- Research involving greater than minimal risk with no prospect of benefit yet likely to yield general knowledge about the subject's disease; or

- Research not otherwise approvable that presents the opportunity to understand, prevent, or ameliorate a serious problem affecting children.

Genomic research presents a variety of potential risks to children, including invasion of privacy and disclosure of unanticipated genetic information. For instance, genetic information could be used to predict ancestral origins, reveal misattributed parentage, or identify health risks. Furthermore, genetic information can be difficult to understand and therefore may be misunderstood or misinterpreted by families. It can also cause stress and anxiety, alter family relationships, or result in stigmatization and discrimination. Ms. Thomson encouraged the group to consider how great—or minimal—these risks are to children and their families.

Nicole Lockhart, Ph.D., NCI OBBR, moderated the interactive discussion that followed, which addressed the risks of genetic research, protections against those risks, and the risks and benefits particularly to children. Projects with large-scale genomics analysis were then discussed in the context of these considerations.

Risks of Genetic Research. Two areas of risk were discussed: Privacy risks that may exist even with controlled access to genetic data and risks associated with other Federal agencies accessing that data. Fewer and fewer data are being put in the public domain, but even with controlled access, privacy cannot be completely guaranteed. The most secure scenario would involve requiring that investigators travel to the physical site where the data are held to mine that data under supervision. While this approach was seen as burdensome and inappropriate for projects with the goal of promoting data sharing, like the NIH genome-wide association studies (GWAS) initiative, workshop participants nevertheless agreed that it may be appropriate to limit public access to some genomic data. One workshop participant noted that many of the discussions surrounding this topic recognize that it may no longer be possible to guarantee complete privacy protection and that the emphasis may need to shift to preventing misuse of genetic data.

Privacy risk was also discussed in the context of criminal investigations. A workshop participant asked whether the U.S. Department of Justice (DOJ) could access genetic data for forensic purposes. A workshop participant reported that under the NIH GWAS policy, data access is granted for research purposes. Therefore, an agency like the DOJ could request access to GWAS data for a research purpose subject to approval of a data access committee and the data access limitations developed by the submitting institution. If an agency requested access to GWAS data for a nonresearch purpose, high-level negotiations would occur between the NIH and the requesting agency, including discussion of the purpose of the data request. Under the current GWAS policy, the NIH does not maintain patient identifiers and would likely resist providing data for forensic purposes to the full extent possible.

Protections Against Privacy Risk. Next, the group discussed protections against privacy risk, including those provided by the Genetic Information Nondiscrimination Act (GINA), which is intended to minimize individual risk by prohibiting use of genetic information for considering eligibility for health insurance or employment. A limitation of GINA is that it does not address disability or long-term care insurance. A workshop participant described a scenario in which laptop computers containing genomic data are stolen and suggested that the risk from discrimination in insurance and employment may be minimized by protections such as GINA.

However, she asked the group to consider the difference between the probability of risk and the probability of actual harm and whether "we are protecting ourselves against unlikely scenarios." Dr. Compton agreed that the probability of actual harm is less in the case of the stolen computers because it takes tremendous IT expertise to do anything with the data but expressed concern that it will become easier to decipher that data and to do harm in the future as IT advances. It is therefore critical to prevent harms in the first place by implementing systems that monitor, protect, and oversee biorepositories.

Risks and Benefits to Children. Discussion on this topic began with workshop participants posing broad questions about genetic research and risks. They asked two questions: What level of risk is the public willing to accept in exchange for personalized medicine? Do we take a cautionary approach and overprotect in the case of pediatric genomic research? A workshop participant argued that pediatric genomic research should proceed only if it presents minimal risk or little more than minimal risk to children, even if this means limiting access to data. Further, he cited a statement issued by the American Academy of Pediatrics Committee on Bioethics in 2001[21] recommending that genetic testing for clinical purposes be conducted in children only if there is known medical intervention for the disease or disorder in question; otherwise, testing should not occur until the child reaches the age of majority and gives consent. Another workshop participant pointed out that parents are nevertheless advocating for genetic testing in situations where there is no known medical intervention but where early counseling and education might be of benefit to the child's health; e.g., fragile X syndrome. A workshop participant reported that the NIH GWAS policy does not offer specific guidance on the sharing of pediatric genetic data although an accompanying Points to Consider document[22] does recommend that the IRB at the submitting institution consider whether genetic data from children should continue to be maintained and shared once the child reaches the age of majority.

Projects With Large-Scale Genomics Analysis. The group was asked to consider what protections would be required to ensure minimal risk to children were their samples to be included in projects with large-scale genomics analysis. Several recommendations were offered by different workshop participants. One recommendation was to engage the community as early as possible in research activities. These activities would focus on the pediatric cancer community, and participants, especially cancer survivors, would be asked how they would assess research risks versus benefits. Other recommendations were to keep pediatric data behind a firewall initially to see what issues arise, to work with the COG that comprises more than 200 IRBs with extensive experience in pediatric specimen banking research activities, to seek assent with children and consent at the age of majority, and to implement processes and protections that minimize risk. One workshop participant suggested that it is unethical not to include pediatric specimens in large-scale genomics analyses because this involves excluding a group—essentially a justice issue. Furthermore, advances in pediatric cancer treatment and diagnosis will not be achieved if pediatric cancer patients are not included in large-scale team science research

[21] Nelson RM et al. Policy Statement: Ethical Issues With Genetic Testing in Pediatrics. *Pediatrics*. 2001;107:1451-1455.

[22] NIH Points to Consider for IRBs and Institutions in their Review of Data Submission Plans for Institutional Certifications Under NIH's Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS). Available at: http://grants.nih.gov/grants/gwas/gwas_ptc.pdf. Accessed March 6, 2009.

projects. Dr. Compton emphasized the need to strike a balance between making data accessible and protecting subjects.

L. Closing Remarks

Dr. Compton thanked workshop participants for their contributions, which will help clarify key issues, identify priorities, and determine the next steps in developing guidance for the use of pediatric biospecimens in research. The OBBR will produce a public meeting summary from the workshop, translate the results into best practices, and develop tools to help biospecimen resources, such as sample informed consent language addressing the use of pediatric biospecimens. Dr. Compton closed the workshop by encouraging attendees to stay involved by continuing to provide input, participating in working groups, and attending future workshops that may be needed to explore these issues further.

National Cancer Institute
Office of Biorepositories and Biospecimen Research
National Institutes of Health

ATTACHMENT 1: WORKSHOP AGENDA
THE ETHICAL USE OF PEDIATRIC BIOSPECIMENS IN RESEARCH

October 24, 2008
8:30 a.m. – 5:00 p.m.

Neuroscience Conference Center
6001 Executive Boulevard
Rockville, Maryland

8:00 a.m.	**Registration and Breakfast**
8:30 a.m.	**Welcome** Carolyn C. Compton, M.D., Ph.D. Director, Office of Biorepositories and Biospecimen Research National Cancer Institute, NIH
8:50 a.m.	**Ethical Perspective on the Use of Pediatric Biospecimens in Research** Robert "Skip" Nelson, M.D., Ph.D. Pediatric Ethicist, Office of Pediatric Therapeutics Food and Drug Administration
9:10 a.m.	**Regulatory Perspective on the Use of Pediatric Biospecimens in Research** Lisa Rooney, J.D. Division of Compliance Oversight Office for Human Research Protections
9:30 a.m.	**IRB Perspective on the Use of Pediatric Biospecimens in Research** Mark Schreiner, M.D. Chair, Committees for the Protection of Human Subjects (IRB) The Children's Hospital of Philadelphia
9:50 a.m.	**Panel Discussion** Robert "Skip" Nelson, M.D., Ph.D. Lisa Rooney, J.D. Mark Schreiner, M.D.
10:20 a.m.	**Coffee Break**

10:40 a.m. **What Do Research Participants Expect from the Consent Process?**

Carol Weil, J.D.
Office for Human Research Protections
On detail at:
Office of Biorepositories and Biospecimen Research
National Cancer Institute, NIH

11:00 a.m. **Practical Perspective on Pediatric Biobanking: The Children's Oncology Group Tissue Bank**

Jay Bowen, M.S.
Biopathology Center
Research Institute at Nationwide Children's Hospital

11:20 a.m. **Panel Discussion**

Jay Bowen, M.S.
Craig Lustig, Executive Director of the Children's Cause for Cancer Advocacy
Paul McKay, President and Director of the Brain Tumor Action Network
Carol Weil, J.D.

11:50 a.m. **Lunch**

1:00 p.m. **Interactive Discussion: Should Consent Be Sought at Age of Majority from Former Pediatric Biospecimen Donors?**

Moderator:
Carol Weil, J.D.

3:00 p.m. **Coffee Break**

3:15 p.m. **Interactive Discussion: Does Genetic Research Present Additional Considerations for the Use of Pediatric Biospecimens?**

Introduction:
Elizabeth Thomson, DNSc, R.N.
National Human Genome Research Institute
National Institutes of Health

Moderator:
Nicole Lockhart, Ph.D.
Office of Biorepositories and Biospecimen Research
National Cancer Institute

4:45 p.m. **Closing Remarks**

5:00 p.m. **Adjourn**