PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Translational Research in Pediatrics: Tissue Sampling and Biobanking

Alayne R. Brisson, Doreen Matsui, Michael J. Rieder and Douglas D. Fraser

Pediatrics; originally published online December 5, 2011;
DOI: 10.1542/peds.2011-0134

Translational Research in Pediatrics: Tissue Sampling and Biobanking

AUTHORS: Alayne R. Brisson, HBSc,[a,b] Doreen Matsui, MD,[b,c] Michael J. Rieder, MD, PhD,[b,c,d] and Douglas D. Fraser, MD, PhD[a,b,c,d,e,f,g]

[a]*Translational Research Centre, London, Ontario, Canada;* [b]*Children's Health Research Institute, London, Ontario, Canada;* [c]*Departments of Pediatrics,* [d]*Physiology and Pharmacology, and* [e]*Clinical Neurologic Sciences, University of Western Ontario, London, Ontario, Canada;* [f]*Centre for Critical Illness Research, London, Ontario, Canada; and* [g]*Canadian Critical Care Translational Biology Group*

KEY WORDS

translational research, pediatrics, tissue repository, biological specimen bank

ABBREVIATIONS

ID—identifier
IRB—institutional review board
REB—research ethics board
SOP—standard operating procedure

Ms Brisson and Drs Matsui, Rieder, and Fraser have made substantial contributions to the conception, content, and revision of the article. All authors approve the article as it has been submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2011-0134

doi:10.1542/peds.2011-0134

Accepted for publication Aug 17, 2011

Address correspondence to Douglas D. Fraser, MD, PhD, Paediatric Critical Care Medicine, Room C2-C82, Children's Hospital, London Health Sciences Centre, 800 Commissioners Rd East, London, ON, Canada, N6A 5W9. E-mail: douglas.fraser@lhsc.on.ca

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

abstract

Translational research is expanding and has become a focus of National Research funding agencies, touted as the primary avenue to improve health care practice. The use of human tissues for research on disease etiology is a pillar of translational research, particularly with innovations in research technologies to investigate the building blocks of disease. In pediatrics, translational research using human tissues has been hindered by the many practical and ethical considerations associated with tissue procurement from children and also by a limited population base for study, by the increasing complexities in conducting clinical research, and by a lack of dedicated child-health research funding. Given these obstacles, pediatric translational research can be enhanced by developing strategic and efficient biobanks that will provide scientists with quality tissue specimens to render accurate and reproducible research results. Indeed, tissue sampling and biobanking within pediatric academic settings has potential to impact child health by promoting bidirectional interaction between clinicians and scientists, helping to maximize research productivity, and providing a competitive edge for attracting and maintaining high-quality personnel. The authors of this review outline key issues and practical solutions to optimize pediatric tissue sampling and biobanking for translational research, activities that will ultimately reduce the burden of childhood disease. *Pediatrics* 2012;129:1–10

Translational research is a process by which research results are made rapidly applicable to the population under study and is ideally bidirectional.[1–3] Knowledge from basic science is used to develop new diagnostics and therapies while clinical insights generate laboratory-testable hypotheses.[4] This directional balance creates an exciting and productive research environment, allowing for better understanding of disease states and fueling the common goal of better patient care.[5,6]

Patient tissue sampling and biobanking is a pillar of translational research, allowing for laboratory investigations on human disease. Tissue biobanking is challenging and requires established infrastructure, standardized protocols, and clinical databases.[1,7] In pediatrics, tissue biobanking involves additional and unique barriers,[1] including small program sizes, fewer investigators, less subjects, unique ethical challenges, a large developmental spectrum, a preponderance of rare illnesses, difficulties in sample-collection methods, and small tissue-sample volumes. Despite these significant obstacles, pediatric biobanks are invaluable for providing scarce human material to meet the needs of child-health investigators for translational research.

In this review, the authors outline key issues and practical solutions for initiation or expansion of pediatric tissue biobanks. Further information on development of biobank networks and creation of standard operating procedures (SOPs) and best practices can be obtained from Web resources (Table 1).

INTEGRATED SERVICES

The integrated services required for optimal tissue sampling and biobanking will depend on the tissue-collection model. Potential models include prospective collection, banking of pathologic specimens, or banking of specimens associated with clinical trials.[8,9] Stored newborn-screening blood samples are also available but subject to research guidelines established by government agencies.[10–12]

Prospective sample collection has proven successful for biorepository growth[8,9] and relies on collection of tissues for prespecified research purposes, with unused portions retained for future research. The prospective model reduces costs of future research by eliminating the collection step, making more projects feasible, and providing for unexpected opportunities.[13] The scope of the specimens must be kept broad and the quality high to accommodate for shifts in research goals over time.[14] Research needs seem unchallenging on service initiation; however, once sampling frequency increases, it is often difficult to manage increasing demands.[8,9]

Regardless of the collection model chosen, integrated services should include bioethical support, consent and assent assistance, and collection of sample-matched clinical data. Services should follow SOPs (Table 2). To aid

TABLE 1 Some Recommended Web Site Resources for Biorepositories

Topic	Web Site	Organization
Best practices	http://www.isber.org/	International Society for Biological and Environmental Repositories
Best practices	http://biospecimens.cancer.gov/bestpractices/	National Cancer Institute
Best practices	http://www.oecd.org/document/50/0,3343,en_2649_34537_1911986_1_1_1_1,00.html	Organisation of Economic Co-operation and Development
Biologics guidance, compliance, and regulatory information	http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm	US Food and Drug Administration
Technical guidelines and requirements	http://www.ich.org/products/guidelines.html	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals in Human Use
Biospecimen research database and information	https://brd.nci.nih.gov/BRN/brnHome.seam	National Cancer Institute Office of Biorepositories and Biospecimen Research
Translational research networking	http://sigs.nih.gov/trig/Pages/default.aspx	National Institutes of Health Translational Research Interest Group
Research networking	http://cordis.europa.eu/	Community Research and Development Information Service for Science, Research and Development
Rare diseases biobank network	http://www.eurobiobank.org/	Euro Bio-Bank
European biobanking infrastructure	http://www.bbmri.eu/	Biobanking and Biomolecular Resources Research Infrastructure
Biobanking information	http://www.esbb.org/	European, Middle Eastern & African Society for Biopreservation & Biobanking
Links to repository information and tools	http://www.p3gobservatory.org/	P3G Observatory
Translational research SOPs and information	http://www.translationalresearch.ca/	Translational Research Centre

All Web sites were accessed in July of 2011.

TABLE 2 Services, SOP Recommendations, and the Resulting Improvements

Service	SOP Recommendation	Result
Labeling of specimens[8]	Use high-quality adhesive labels	Prevents label separation
	Avoid handwritten labels	Allows better readability
	Provide human-readable and barcode format of unique ID on each specimen[39]	Prevents mislabeling
Specimen collection	Have personnel present at collection	Reduces lag time and bias
	Use same collection vessels between samples	Reduces bias between samples[43,44,61–64]
	Perform collection at the same time as clinical samples	Provides more data to store with each sample; less invasive
	Schedule sample collection to correlate with ideal shipping times	Reduces shipments on nonbusiness days to avoid frozen sample loss caused by thawing
Specimen processing	Process rapidly after collection and keep lag time constant	Reduces changes within the sample and increases quality[14,65]
	Use the same temperature, centrifugal force, centrifugation time, and aliquot sizes between samples	Prevents bias between samples
	Create aliquots up front	Avoids freeze-thaw cycles
	Use 0.25-mL aliquot vol for fluids	Provides large enough vol for most assays while minimizing waste upon thawing[8]
Specimen storage	Use the same storage vessels (cryovials with silicone gasket recommended) and time from processing to freezing between samples	Prevents bias between samples
	Use small storage vessels	Maximizes storage space[13]
	Store at ultra-low temperature (−70°C or lower)	Allows longer storage times without changes in specimen[66]
	Store sample aliquots in multiple locations	Reduces sample loss in case of equipment failure
	Use detailed storage location documentation	Allows ease of retrieval
Specimen shipment	Use licensed couriers	Increases reliability and accountability
	Use enough cooling materials (eg, dry ice) for multiple days	Prevents specimen thawing
	Keep shipment notification and shipment log	Ensures all samples are tracked and properly delivered
General	Use endotoxin-free materials	Prevents changes within specimen
	Take detailed notes at every step	Increases value of specimen and accounts for bias
	Use personal protective equipment	Increases personnel safety

investigators with analytical services, partnerships should be generated with facilities capable of histology, immunoanalysis, genomics, and proteomics. Epidemiology and biostatistics connections are important, as is external biobank collaboration to aid the collection of, and access to, rare specimens.

ETHICS AND INFORMED CONSENT

Tissue sampling and biobanking must be approved by the presiding institutional review board (IRB) or research ethics board (REB). Biorepository personnel should have ongoing communication with the IRB or REB,[15] and investigators must be familiar with local IRB and REB policies. Tissue specimens must be specified for valid biomedical research and not other purposes such as commercial gain, political reasons (eg, advancement of criminal-investigation techniques and paternity tests or for immigration purposes), or for purely technical purposes.[16,17]

A biorepository committee comprising clinicians or scientists who are familiar with the needs of the translational research community should be formed to ensure the ethical and scientific validity of projects requiring samples.[18–20]

Provision of bioethical support is critical to assist investigators with completion of ethics-review documents, including details of sample collection and processing, de-identification methods, storage, and off-site shipment. A potential approach to explore with the respective IRB or REB is for the biorepository to append its IRB/REB approval to individual investigators' protocols. Investigators also may require assistance with consent and assent once eligible participants or their legal guardians are identified and approached by their clinician. Involvement of experienced biorepository staff in the consent process is advantageous because it avoids potential conflicts of interest and the appearance of coercion by investigators.[15,21]

IRBs and REBs have differing views on participants giving broad consent for future use of their specimens in research.[16,17,22,23] Consent for a single study jeopardizes the amount and quality of research that can be performed on a particular sample,[16] whereas broad consent allows multiple studies to use stored specimens. Most citizens are willing to give broad consent for research so long as the future use is approved by an IRB or REB.[16] Separate letters of information and consent for the biorepository and current investigation clarify to potential participants the intended use of their samples. Participants must be informed of potential genetic analyses on stored material and must be able to opt-out or be excluded from a study. DNA analysis can create special concerns, although this issue may be less germane for somatic mutations, such as those associated with cancer, rather than genetic mutations.[24,25]

Concerns include possible future genetic discrimination by employers or insurance companies.[25]

Typically, there is increased scrutiny for projects involving children.[15,21] Proxy consent must be obtained, and one must consider the involvement of the child in providing assent.[26] A complicating factor is the different age range considered appropriate for assent in different jurisdictions and special issues with respect to assent in adolescents. Emancipated or mature minors may be able to consent for themselves, depending on local laws.[27] IRBs and REBs may require assent from children >7 years of age[21]; however, in 1 study it appeared that many children do not understand the concept of a biorepository.[26] Because the risk is minimal in most cases, assent may not be routinely necessary, although further investigation is required. Given enough information, parents or legal guardians should be able to make a proper assessment of benefits and risks for their children.[28–30]

As a temporarily vulnerable population, children reserve the right to withdraw specimens from the tissue bank at any time after they reach the age of consent[16]; however, requesting consent from adults for the ongoing use of their specimens collected in childhood is thought unrealistic.[31] The authors of 1 study concluded that children are generally trusting of their parents' decisions and have little concern over continued use of their specimens and data.[32] Parents should be advised to make information available to their children so that they can determine how they would like their samples to be used when they are adults.

When providing samples and matching clinical data to investigators, special care must be taken to maintain the privacy, confidentiality, and cultural sensitivities of children.[33] General findings from studies may be shared with families (including non-donors), and clinically relevant results may be shared with the participants, their physicians, and parents.[24,25] Disclosure of information to parents may be considered a breach of autonomy because it prevents the child from exercising the right not to know, a choice a child might make as an adult.[25] Returning information from research analyses often is hindered by time lapse.[24]

Deferred consent may be considered under special circumstances (eg, critically ill patients) and when collection times are crucial. If risk is minimal and the legally authorized representative is not present initially, the sample can be taken and informed consent can be obtained post-hoc (ie, within 24 hours). If consent is not subsequently obtained, the samples and data collected must be destroyed.

RESOURCES

Upfront costs for a biorepository include office and laboratory space, equipment, tissue-storage systems, a clinical database, and personnel. Ongoing costs include equipment maintenance and replacement, laboratory supplies, and operating expenses for which continued funding must be available.[9]

Infrastructure

The biorepository is located ideally within an academic hospital for patient access, clinical and research support, rapid collection and processing times, and elimination of tissue transfer offsite. The space must have level-2 biosafety approval, with directional airflow or use of a biological safety cabinet, and it must be accessible only to designated personnel. When studies involve samples from patients with potentially lethal infectious agents, level-3 approval is required.[34] Major equipment required at the outset includes a lockable, alarmed freezer (−70°C or lower); a refrigerated centrifuge with sealed buckets; a refrigerator-freezer; and computer equipment. If the cross-contamination risk is low, the laboratory can share existing resources at the hospital or institution, including wet or dry ice, biological safety cabinets, and autoclaves. Other supplies are specific to the types of tissues being collected.[9,35]

With respect to cryogenic storage systems, smaller biorepositories may store samples in 0.5- to 2.0-mL cryovials with high-quality, laboratory printer–generated labels. For larger-scale biorepositories, two-dimensional barcode systems are available that can automate storage and retrieval, reduce human error, increase efficiency, and provide tubes and storage racks that are more space-saving. Software packages accompany these systems to document and verify storage information and hold sample data. Human-readable labels should be used on tubes because samples might become disorganized or transferred to laboratories without barcode scanners.

Personnel

A biorepository director familiar with both clinical and research aspects of translational research should be appointed. A major responsibility of the director is to foster communication and collaboration between laboratory scientists and clinicians. At the outset, the director contributes a considerable amount of his or her time to the facility.[9]

An experienced research manager should be appointed to direct daily activities and should be familiar with human-tissue handling, biosafety, shipping regulations, and site-specific health and safety issues. The research manager also might collect, process, and ship specimens; maintain the database; order supplies; update the budget; and revise the SOPs. Frequent interactions between the research manager and investigators optimize the research environment. If need or demand is

sufficient, a pediatric-trained nurse or phlebotomist may be required.

Funding, Business Plan, and Cost Recovery

Ideally, biorepository services are not charged to local academic investigators, although additional funding often is required.[8] Funding sources include government-infrastructure granting agencies, academic or institutional core facility funds, or use of a foundation or charitable trust.[36] If funded by commercial partners, source publication renders potential conflicts of interest transparent. Public funding sources also should be reported, even if they arise from commercial parties. A business plan should be developed, identifying the goals of the center, its location and infrastructure, whom the center will be marketed to, services provided, personnel required, markers of success, and a 3- to 5-year budget.

Beyond initial start-up costs, many repositories fail to sustain ongoing funding. To prevent premature closure, it is important to campaign for institutional support from the beginning.[14] To demonstrate the value of the service, researchers who do not pay the actual costs of sample collection are invoiced, with the total billed shown as 0 so they will be aware of the actual costs of tissue procurement and storage and are more likely to be advocates for the biorepository.[14]

Cost recovery may be targeted at industry-based trials and, if need be, academic researchers requesting stored biorepository samples. Multiple methods exist for determining fees (Table 3). For large-scale repositories, cost per sample from the time of collection to shipping was estimated to be between US $60 and US $150.[37] In all cases, robust economic evaluations are encouraged to determine if key costs (eg, equipment maintenance and renewal) are included in the overall cost estimates.

SOPs

Standardized procedures for tissue collecting and biobanking are crucial for creating greater stability within and between samples and for preventing bias. Downstream applications should be considered when developing SOPs, and SOPs should be reviewed and updated regularly. SOPs also can be obtained through collaboration with preexisting biobanking facilities, biomarker networks, or trial groups (Table 1), but adapted SOPs typically require alteration to reflect the challenges of pediatric biobanking. Pilot studies may be required to create SOPs when the research goals are specific. SOPs and best practices for biorepositories are outlined in Tables 2 and 4.[8,38–40]

To maximize research productivity from limited tissue samples,[13] SOPs should be developed based on best practices and the needs of local investigators, while having a broad scope for sample viability in future research. In general, plasma is more biologically relevant than serum, because serum clotting can affect biomarker concentrations,[14,41–44] and it is imperative to minimize processing times and avoid freeze-thaw cycles.

TISSUE SAMPLES AND COLLECTION METHODS

Determination of the types of tissues to be collected (Table 4) establishes the services provided, the storage methods used, and the specific equipment and supplies needed.[8] For pediatrics, study design should include less invasive specimen types, including saliva, cord blood, and urine.[13,33] Attempts should be made to collect research samples at the same time as those for clinical purposes,[27,33] making it clear to potential participants that extra samples are being taken for research. In pediatrics, the vol or size of specimens is generally less than that obtained from adults, and often little specimen material remains for biobanking purposes.

Children participating in research should have specimens obtained in a friendly environment and by someone who is experienced in techniques applicable to children,[27,45] so the child does not become procedure-phobic.[46] Pediatric nurses or phlebotomists who are familiar with the coping mechanisms and distress signals of children are required. Bad experiences perceived by children result in greater distress with each visit,[46] making procedures difficult.[47] Indeed, some children will not consent to be in a research study because of fear of phlebotomy.[48]

Research blood procurement should pose no increased risk for complications greater than that of standard

TABLE 3 Methods of Determining Sample-Related Costs After Initial Start-up of Biorepository

Method	Required Input	Pros and Cons
Actual cost: sum all sample-related costs and divide by number of samples over a period of time	Supplies (disposables per sample); Personnel time (h per sample); Equipment costs (maintenance); Facility charges (overhead, waste disposal)	Difficult to assess at outset; Regular updating required; Best estimate of actual costs
Charge similarly to hospital laboratory	Pricing from local hospital core laboratory	Price reflects cost of processing only; Other sample costs underestimated; Quick and efficient way to get base prices
Set cost similar to that of a research animal[8]	Research prices of publically available animal models (murine)	Comparable cost for investigators; May not relate to actual costs of sample

TABLE 4 Types of Specimens Commonly Collected for Translational Research

Specimen	Collection Methods	Recommendations
Blood[13,67–72]	Venipuncture (best practice) Cannulae	Fill vacutainers to fill line to reduce blood to additive variations; Store plasma because it is more biologically relevant than serum[73]; Use the same additives and tube types between samples[43,63]; Collect venous rather than arterial samples[74] and do not collect capillary samples; Collect samples from circulating blood vol and not reservoirs (catheters or other devices)[52]; Maintain samples on ice and centrifuge at 4°C
Urine[13,69,75]	Direct void (best practice) Catheter	Maintain samples on ice and centrifuge at 4°C; May require preservative; Consider time of collection
Saliva[76–80]	Buccal swab; Void directly into container	Use commercial products to ensure stability (for genomics); Use same collection method for all samples; Test collection methods for biomarker of interest before banking
Cerebrospinal fluid[81]	Lumbar puncture; External ventricular drain	Maintain samples on ice and centrifuge at 4°C; Centrifuge samples to eliminate contaminants; Use the same draw vol to prevent bias
Bronchoalveolar lavage[82]	Bronchoscopy or blind sampling	Take specimens at same time as diagnostic testing and use only fresh material; Retrieve as much bronchoalveolar lavage specimen as possible for research without interfering with diagnostics; Place on ice immediately and perform all processing at 4°C; Handle open samples in biological safety cabinets and process in laboratory with proper containment level for suspected pathogens; Record volumes at centrifugation steps
Biopsy[35] and solid tissue[83,84]	Surgery; Endoscopic procedures	Freezing allows for greater diversity of downstream applications compared with fixation[85–87]; Snap-freeze immediately after excision; Should not interfere with diagnostic specimens; Divide into several sections before freezing; Formalin-fixed, paraffin-embedded tissues only when requested by investigator, can collect both types from same sample[38,83]

clinical venipuncture. Maximum daily and monthly amounts of blood that may be drawn from pediatric patients are listed in Table 5.[33,45] Vacuum blood-collection tubes should be used only on older children because they can cause veins to collapse and stoppage of blood flow in young children.[46,49] Butterfly needles are recommended for better control if the child moves during the procedure.[46] Using a syringe to collect blood, with alternating gentle suction-and-release method, will allow veins to refill[46] and also may prevent hemolysis.[8] Blood collection from ill pediatric patients raises concerns of inducing or aggravating anemia.[50,51] Pediatric small-vol blood tubes (0.5–3.0 mL) should be used, and care should be taken to obtain suitable specimens the first time to minimize repeated sampling. Intravascular catheters should be considered if clinically indicated, and frequent sampling is required.[52]

CONTROL-SPECIMEN COLLECTION

Ideally, control-specimen collection is ongoing, because the availability of biorepository control specimens enables samples to be shared among researchers and reduces burden on volunteers. Identical SOPs should be used to collect control and study specimens, reducing bias (Table 2), and any variables affecting sampling conditions must be documented. Splitting samples into both plasma and serum ensures availability for a wider number of research applications.

Lack of age- and gender-matched control specimens is a critical limitation for many pediatric studies. Generally, control specimens from healthy volunteers are collected from older children who are able to give assent; however, this practice poses a problem in matching samples to those from younger children with unique clinical variables.[41] An alternative option for younger children includes sample collection immediately after anesthesia induction for minor surgical procedures in otherwise healthy children.

Healthy volunteers may not always be the most suitable reference population.[41] Study-specific control samples matching the disease state and background of the patient may be more

TABLE 5 Maximum Amounts of Blood To Be Drawn From Children Younger Than 14 Years

Patient's Wt, kg	Maximum Amount To Be Drawn at 1 Time, mL	Maximum Amount To Be Drawn During 1 Mo, mL
<2.7[a]	0.8	2.4
2.7–3.6	2.5	23
3.6–4.5	3.5	30
4.5–6.8	5	40
7.3–18.2	10	60–130
18.6–27.3	20	140–200
27.7–29.5	25	220
30.0–45.5	30	240–350

Adapted from Buckbee.[45]

[a] Amounts for preterm and term neonates (European Union guidelines[33]).

applicable. For example, a control sample to match with a patient on a ventilator with septic shock could be from someone free of infection who is also ventilated and receiving sedative medications. Drug-matched control specimens may be required when adverse drug effects are studied. In the research of rare, heritable diseases it is ideal to obtain samples from family members of those affected, and the biobank personnel can oversee simultaneous collection of these samples because parents often accompany their children.

CLINICAL DATA COLLECTION AND STORAGE

Clinical data linkage with tissue specimens is critical for personalized medicine.[53] To increase the biological value of each specimen, adequate clinical information should be obtained at the time of collection.[13,14,54] The patient data collected will vary according to the study, and common variables are summarized in Table 6. At a minimum, the following preanalytical details should be collected: specimen type, SOP (and any deviations), collection date and time, sample vol (or mass for solid tissues), collection container, processing time, freezing time, and collection site.[8]

Data storage can be accomplished with a pre-existing database[55–57] or by using commercial software that accompanies cryogenic storage systems. The database interface should allow for collection of equivalent information for each sample to reduce variability, and it should be user-friendly.[8] A vocabulary for the database should be created so that samples can be matched efficiently and reliably. Biorepository vocabulary is unique because there is generally different information needed to identify samples compared with clinical vocabulary.[8] Coding also may be used to describe preanalytical procedures and variables.[58]

The database should be adaptable for incorporation of extra data, and it should track significant events such as sample thaws, loss, destruction, processing of any kind, and distribution.[39] When using a barcode system, the database must be capable of assigning a unique identifier (ID) to samples and tracking the other IDs required (specimen ID, subject ID, protocol ID, and so forth). Care must be taken not to overwrite or repeat IDs.

The database should be Web-accessed and password-protected so that information is remotely and safely accessible. Investigators are provided a unique access code, allowing them access to information particular to their project. The interface should be intuitive and generate reports summarizing data. All data available to investigators must be de-identified. To decrease the risk of patient identification, databases holding confidential patient information must meet the requirements of the Health Insurance Portability and Accountability Act[59] or equivalent. Generally, this requirement includes encryption, firewalls, unique access codes, and audit trails.

Sharing of tissue samples and clinical data has the possibility to increase research productivity, especially in the case of rare diseases. When biobanked samples and clinical data are shared, however, the donors have decreased control over their stored specimens and matched clinical information, including the inability to withdraw consent.[60] Local investigators should be consulted early to identify their research needs, and data-sharing policies should be described in the consent document.

TABLE 6 Recommended Patient Information To Be Collected With Research Samples

Type	Information
Research study	Current study; Additional studies in which patient is involved
Illnesses or injuries	Current; Past; Family history
Demographics	Age; Gender; Race (can include Native, Asian, black, white); Height; Wt (birth wt for neonates)[52]; Head circumference; Gestational age (infants)
Vital signs at time of sampling (when available)	Heart rate; Respiratory rate; Blood pressure; Temperature; Mean arterial pressure; Pulse oxygen saturation
Ventilation records (when ventilated)	Type of ventilation; Mode; Fraction of inspired oxygen; Mode-specific variables
Clinical laboratory reports (corresponding to research sample)	Blood tests; Urine tests; Cerebrospinal fluid culture specimens
Medication profiles	Drug name; Dosage; Route of administration; Frequency
Comorbidities	General category; Specific
Surgical information	Current; Past
Healthy volunteer information	Age; Gender; Medications; Health history

CONCLUSIONS

Tissue sampling and biobanking is a pillar of translational research, but it is currently underutilized in child health research. A successful biorepository must be supported by a critical mass of investigators, have a significant infrastructure for continuous growth, and should adhere strictly to SOPs. Biorepository utilization can facilitate high-quality translational research, decrease time to discovery, and ultimately, improve child health.

ACKNOWLEDGMENTS

This study was supported by the Children's Health Foundation (http://www.childhealth.ca; London, Ontario) and the Lawson Health Research Institute (https://www.lawsonresearch.com; London, Ontario).

REFERENCES

1. Szilagyi PG. Translational research and pediatrics. *Acad Pediatr*. 2009;9(2):71–80
2. Zerhouni E. Medicine. The NIH roadmap. *Science*. 2003;302(5642):63–72
3. Plebani M, Marincola FM. Research translation: a new frontier for clinical laboratories. *Clin Chem Lab Med*. 2006;44(11):1303–1312
4. Marincola FM. Translational medicine: a two-way road. *J Transl Med*. 2003;1(1):1
5. Mankoff SP, Brander C, Ferrone S, Marincola FM. Lost in translation: obstacles to translational medicine. *J Transl Med*. 2004;2(1):14
6. Roman J. Creating a culture of discovery through clinical trials and translational research. *Am J Med Sci*. 2009;337(3):155
7. Boat TF. The future of pediatric research. *J Pediatr*. 2007;151(suppl 5):S21–S27
8. Bell WC, Sexton KC, Grizzle WE. Organizational issues in providing high-quality human tissues and clinical information for the support of biomedical research. *Methods Mol Biol*. 2010;576:1–30
9. Grizzle WE, Aamodt R, Clausen K, LiVolsi V, Pretlow TG, Qualman S. Providing human tissues for research: how to establish a program. *Arch Pathol Lab Med*. 1998;122(12):1065–1076
10. Couzin-Frankel J. Newborn blood collections. Science gold mine, ethical minefield. *Science*. 2009;324(5924):166–168
11. Vladutiu GD. Considerations and recommendations for national guidance regarding the retention and use of residual dried blood spots specimens after newborn screening. *Mol Genet Metab*. 2010;101(2-3):93–94
12. Haga SB. Analysis of educational materials and destruction/opt-out initiatives for storage and use of residual newborn screening samples. *Genet Test Mol Biomarkers*. 2010;14(5):587–592
13. Holland NT, Pfleger L, Berger E, Ho A, Bastaki M. Molecular epidemiology biomarkers—sample collection and processing considerations. *Toxicol Appl Pharmacol*. 2005;206(2):261–268
14. Riegman PH, Morente MM, Betsou F, de Blasio P, Geary P; Marble Arch International Working Group on Biobanking for Biomedical Research. Biobanking for better healthcare. *Mol Oncol*. 2008;2(3):213–222
15. Davidson AJ, O'Brien M. Ethics and medical research in children. *Paediatr Anaesth*. 2009;19(10):994–1004
16. Hansson MG, Dillner J, Bartram CR, Carlson JA, Helgesson G. Should donors be allowed to give broad consent to future biobank research? *Lancet Oncol*. 2006;7(3):266–269
17. Bauer K, Taub S, Parsi K. Ethical issues in tissue banking for research: a brief review of existing organizational policies. *Theor Med Bioeth*. 2004;25(2):113–142
18. Morente MM, Fernández PL, de Alava E. Biobanking: old activity or young discipline? *Semin Diagn Pathol*. 2008;25(4):317–322
19. Yassin R, Lockhart N, González del Riego M, et al. Custodianship as an ethical framework for biospecimen-based research. *Cancer Epidemiol Biomarkers Prev*. 2010;19(4):1012–1015
20. Lemrow SM, Colditz GA, Vaught JB, Hartge P. Key elements of access policies for biorepositories associated with population science research. *Cancer Epidemiol Biomarkers Prev*. 2007;16(8):1533–1535
21. Afshar K, Lodha A, Costei A, Vaneyke N. Recruitment in pediatric clinical trials: an ethical perspective. *J Urol*. 2005;174(3):835–840
22. Hofmann B. Broadening consent—and diluting ethics? *J Med Ethics*. 2009;35(2):125–129
23. Hansson MG. Ethics and biobanks. *Br J Cancer*. 2009;100(1):8–12
24. Ries NM, LeGrandeur J, Caulfield T. Handling ethical, legal and social issues in birth cohort studies involving genetic research: responses from studies in six countries. *BMC Med Ethics*. 2010;11(1):4
25. Hens K, Nys H, Cassiman JJ, Dierickx K. Genetic research on stored tissue samples from minors: a systematic review of the ethical literature. *Am J Med Genet A*. 2009;149A(10):2346–2358
26. John T, Hope T, Savulescu J, Stein A, Pollard AJ. Children's consent and paediatric research: is it appropriate for healthy children to be the decision-makers in clinical research? *Arch Dis Child*. 2008;93(5):379–383
27. Food and Drug Administration, HHS. International Conference on Harmonisation; guidance on E11 clinical investigation of medicinal products in the pediatric population; availability. Notice. *Fed Regist*. 2000;65(242):78493–78494
28. Tait AR, Voepel-Lewis T, Malviya S. Factors that influence parents' assessments of the risks and benefits of research involving their children. *Pediatrics*. 2004;113(4):727–732
29. Rothmier JD, Lasley MV, Shapiro GG. Factors influencing parental consent in pediatric clinical research. *Pediatrics*. 2003;111(5 pt 1):1037–1041
30. Neidich AB, Joseph JW, Ober C, Ross LF. Empirical data about women's attitudes towards a hypothetical pediatric biobank. *Am J Med Genet A*. 2008;146(3):297–304
31. Gurwitz D, Fortier I, Lunshof JE, Knoppers BM. Research ethics. Children and population biobanks. *Science*. 2009;325(5942):818–819
32. Goldenberg AJ, Hull SC, Botkin JR, Wilfond BS. Pediatric biobanks: approaching informed consent for continuing research after children grow up. *J Pediatr*. 2009;155(4):578–583
33. European Union. Ethical considerations for clinical trials on medicinal products conducted with the paediatric population. *Eur J Health Law*. 2008;15(2):223–250
34. World Health Organization. *Laboratory Biosafety Manual*. 3rd ed. Geneva, Switzerland: World Health Organization; 2004:186
35. Leek R. Frozen biopsy collection and storage: frozen biopsy samples. *Methods Mol Med*. 2006;120:25–28
36. Ravid R. Standard operating procedures, ethical and legal regulations in BTB (Brain/Tissue/Bio) banking: what is still missing? *Cell Tissue Bank*. 2008;9(3):151–167
37. Eiseman E, Bloom G, Brower J, Clancy N, Olmsted SS. *Case Studies of Existing Human Tissue Repositories: "Best Practices" for a Biospecimen Resource for the Genomic and Proteomic Era*. Arlington, VA: The RAND Corporation; 2003
38. Troyer D. Biorepository standards and protocols for collecting, processing, and storing human tissues. *Methods Mol Biol*. 2008;441:193–220
39. ISBER. Collection, storage, retrieval and distribution of biological materials for repositories. *Cell Preserv Technol*. 2008;6(1):3–58
40. Betsou F, Barnes R, Burke T, et al; International Society for Biological and Environmental Repositories (ISBER) Working Group on Biospecimen Science. Human biospecimen research: experimental protocol and quality control tools. *Cancer Epidemiol Biomarkers Prev*. 2009;18(4):1017–1025
41. Schrohl AS, Würtz S, Kohn E, et al. Banking of biological fluids for studies of disease-associated protein biomarkers. *Mol Cell Proteomics*. 2008;7(10):2061–2066
42. Albrethsen J, Bøgebo R, Olsen J, Raskov H, Gammeltoft S. Preanalytical and analytical variation of surface-enhanced laser desorption-ionization time-of-flight mass spectrometry of human serum. *Clin Chem Lab Med*. 2006;44(10):1243–1252
43. Banks RE, Stanley AJ, Cairns DA, et al. Influences of blood sample processing on

low-molecular-weight proteome identified by surface-enhanced laser desorption/ionization mass spectrometry. *Clin Chem*. 2005;51(9):1637–1649

44. Yucel A, Karakus R, Cemalettin A. Effect of blood collection tube types on the measurement of human epidermal growth factor. *J Immunoassay Immunochem*. 2007;28(1):47–60
45. Buckbee KM. Implementing a pediatric phlebotomy protocol. *MLO Med Lab Obs*. 1994;26(4):32–35
46. Willock J, Richardson J, Brazier A, Powell C, Mitchell E. Peripheral venepuncture in infants and children. *Nurs Stand*. 2004;18(27):43–50; quiz 52, 55–56
47. Thurgate C, Heppell S. Needle phobia—changing venepuncture practice in ambulatory care. *Paediatr Nurs*. 2005;17(9):15–18
48. Dlugos DJ, Scattergood TM, Ferraro TN, Berrettinni WH, Buono RJ. Recruitment rates and fear of phlebotomy in pediatric patients in a genetic study of epilepsy. *Epilepsy Behav*. 2005;6(3):444–446
49. Caws L, Pfund R. Venepuncture and cannulation on infants and children. *J Child Health Care*. 1999;3(2):11–16
50. Bateman ST, Lacroix J, Boven K, et al; Pediatric Acute Lung Injury and Sepsis Investigators Network. Anemia, blood loss, and blood transfusions in North American children in the intensive care unit. *Am J Respir Crit Care Med*. 2008;178(1):26–33
51. Broder-Fingert S, Crowley WF, Jr,Boepple PA. Safety of frequent venous blood sampling in a pediatric research population. *J Pediatr*. 2009;154(4):578–581
52. Guidance for Industry. *General Considerations of Pediatric Pharmacokinetic Studies for Drugs and Biological Products*. Rockville, MD: Food and Drug Administration; 1998:1–12
53. Bathe OF. Molecular determinants of outcomes: linking tissue banks to outcomes databases. *J Surg Oncol*. 2009;99(8):513–516
54. Riegman PH, Dinjens WN, Oosterhuis JW. Biobanking for interdisciplinary clinical research. *Pathobiology*. 2007;74(4):239–244
55. Wang X, Liu L, Fackenthal J, et al. Translational integrity and continuity: personalized biomedical data integration. *J Biomed Inform*. 2009;42(1):100–112
56. Mirhaji P, Zhu M, Vagnoni M, Bernstam EV, Zhang J, Smith JW. Ontology driven integration platform for clinical and translational research. *BMC Bioinformatics*. 2009;10(suppl 2):S2
57. Viangteeravat T, Brooks IM, Smith EJ, et al. Slim-prim: a biomedical informatics database to promote translational research. *Perspect Health Inf Manag*. 2009;6:6
58. Betsou F, Lehmann S, Ashton G, et al; International Society for Biological and Environmental Repositories (ISBER) Working Group on Biospecimen Science. Standard preanalytical coding for biospecimens: defining the sample PREanalytical code. *Cancer Epidemiol Biomarkers Prev*. 2010;19(4):1004–1011
59. US Department of Health and Human Services. Health Insurance Portability and Accountability Act of 1996. Washington, DC: US Government Printing Office; 1996
60. Hawkins AK. Biobanks: importance, implications and opportunities for genetic counselors. *J Genet Couns*. 2010;19(5):423–429
61. Jung K, Klotzek S, Stephan C, Mannello F, Lein M. Impact of blood sampling on the circulating matrix metalloproteinases 1, 2, 3, 7, 8, and 9. *Clin Chem*. 2008;54(4):772–773
62. Preissner CM, Reilly WM, Cyr RC, O'Kane DJ, Singh RJ, Grebe SK. Plastic versus glass tubes: effects on analytical performance of selected serum and plasma hormone assays. *Clin Chem*. 2004;50(7):1245–1247
63. Bowen RA, Hortin GL, Csako G, Otañez OH, Remaley AT. Impact of blood collection devices on clinical chemistry assays. *Clin Biochem*. 2010;43(1-2):4–25
64. Randall SA, McKay MJ, Molloy MP. Evaluation of blood collection tubes using selected reaction monitoring MS: implications for proteomic biomarker studies. *Proteomics*. 2010;10(10):2050–2056
65. Ostroff R, Foreman T, Keeney TR, Stratford S, Walker JJ, Zichi D. The stability of the circulating human proteome to variations in sample collection and handling procedures measured with an aptamer-based proteomics array. *J Proteomics*. 2010;73(3):649–666
66. Pieragostino D, Petrucci F, Del Boccio P, et al. Pre-analytical factors in clinical proteomics investigations: impact of ex vivo protein modifications for multiple sclerosis biomarker discovery. *J Proteomics*. 2010;73(3):579–592
67. Austin MA, Ordovas JM, Eckfeldt JH, et al. Guidelines of the National Heart, Lung, and Blood Institute Working Group on Blood Drawing, Processing, and Storage for Genetic Studies. *Am J Epidemiol*. 1996;144(5):437–441
68. Elliott P, Peakman TC; UK Biobank. The UK Biobank sample handling and storage protocol for the collection, processing and archiving of human blood and urine. *Int J Epidemiol*. 2008;37(2):234–244
69. Holland NT, Smith MT, Eskenazi B, Bastaki M. Biological sample collection and processing for molecular epidemiological studies. *Mutat Res*. 2003;543(3):217–234
70. Tuck MK, Chan DW, Chia D, et al. Standard operating procedures for serum and plasma collection: Early Detection Research Network Consensus Statement Standard Operating Procedure Integration Working Group. *J Proteome Res*. 2009;8(1):113–117
71. Vaught JB. Blood collection, shipment, processing, and storage. *Cancer Epidemiol Biomarkers Prev*. 2006;15(9):1582–1584
72. Tammen H. Specimen collection and handling: standardization of blood sample collection. *Methods Mol Biol*. 2008;428:35–42
73. Drake SK, Bowen RA, Remaley AT, Hortin GL. Potential interferences from blood collection tubes in mass spectrometric analyses of serum polypeptides. *Clin Chem*. 2004;50(12):2398–2401
74. Yang ZW, Yang SH, Chen L, Qu J, Zhu J, Tang Z. Comparison of blood counts in venous, fingertip and arterial blood and their measurement variation. *Clin Lab Haematol*. 2001;23(3):155–159
75. Papale M, Pedicillo MC, Thatcher BJ, et al. Urine profiling by SELDI-TOF/MS: monitoring of the critical steps in sample collection, handling and analysis. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2007;856(1-2):205–213
76. Granger DA, Kivlighan KT, Fortunato C, et al. Integration of salivary biomarkers into developmental and behaviorally-oriented research: problems and solutions for collecting specimens. *Physiol Behav*. 2007;92(4):583–590
77. Sivakumar T, Hand AR, Mednieks M. Secretory proteins in the saliva of children. *J Oral Sci*. 2009;51(4):573–580
78. Kidd S, Midgley P, Lone N, et al. A reinvestigation of saliva collection procedures that highlights the risk of potential positive interference in cortisol immunoassay. *Steroids*. 2009;74(8):666–668
79. Gröschl M, Köhler H, Topf HG, Rupprecht T, Rauh M. Evaluation of saliva collection devices for the analysis of steroids, peptides and therapeutic drugs. *J Pharm Biomed Anal*. 2008;47(3):478–486
80. Rogers NL, Cole SA, Lan HC, Crossa A, Demerath EW. New saliva DNA collection method compared to buccal cell collection techniques for epidemiological studies. *Am J Hum Biol*. 2007;19(3):319–326
81. Teunissen CE, Petzold A, Bennett JL, et al. A consensus protocol for the standardization of cerebrospinal fluid collection and biobanking. *Neurology*. 2009;73(22):1914–1922
82. Health Protection Agency. Investigation of bronchoalveolar lavage, sputum and associated specimens. *National Standard Method*.

2009;BSOP 57(2.3). Available at: www.hpa-standardmethods.org.uk/documents/bsop/pdf/bsop57.pdf

83. Diaz JI, Cazares LH, Semmes OJ. Tissue sample collection for proteomics analysis. *Methods Mol Biol.* 2008;428:43–53
84. Mager SR, Oomen MH, Morente MM, et al. Standard operating procedure for the collection of fresh frozen tissue samples. *Eur J Cancer.* 2007;43(5):828–834
85. Penland SK, Keku TO, Torrice C, et al. RNA expression analysis of formalin-fixed paraffin-embedded tumors. *Lab Invest.* 2007;87(4):383–391
86. Jackson DP, Lewis FA, Taylor GR, Boylston AW, Quirke P. Tissue extraction of DNA and RNA and analysis by the polymerase chain reaction. *J Clin Pathol.* 1990;43(6):499–504
87. Frank M, Döring C, Metzler D, Eckerle S, Hansmann ML. Global gene expression profiling of formalin-fixed paraffin-embedded tumor samples: a comparison to snap-frozen material using oligonucleotide microarrays. *Virchows Arch.* 2007;450(6):699–711

Translational Research in Pediatrics: Tissue Sampling and Biobanking

Alayne R. Brisson, Doreen Matsui, Michael J. Rieder and Douglas D. Fraser

Pediatrics; originally published online December 5, 2011;
DOI: 10.1542/peds.2011-0134