The "Federated Pediatric BioCloud" Model: State of the Art and Future Prospects in Pediatric Biospecimen Science

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Systematic collection, storage of, and access to high-quality biospecimens representative of the various stages of disease remains a great challenge. This remains the case notwithstanding the identification of key issues effecting systemization of tissue handling activity for research using hospital sample archives or siloed institutional biobanks.[1] According to a survey study conducted among US biorepositories in 2013, 44% reported storing biospecimens from children 18 years or under, but only 2% focused solely on the biobanking of pediatric specimens.[2]

Diagnostic sample procurement in a hospital-integrated setting is a clinically driven necessity that often results in remaining material suitable for future research. Such material is typically housed in pathology archives and resourced for conventional biomarker studies because it is the most convenient retrospectively collected source for researchers to explore. Biobanking services have been built on this activity in many hospitals and is a proven model for tissue procurement for a range of studies. Alternatively, prospective biobanking provides a model wherein the research protocol and associated aims drive sample procurement, with participant enrollment specifically targeted toward the establishment of a clinically well-phenotyped disease-specific (or healthy individual) biospecimen bank. The models are rarely capable of providing sufficient study material on their own; therefore, laboratory reference ranges for children remain to be extrapolated from adult populations, barriers remain to pharmaceutical development of targeted therapies with an associated lack of companion diagnostic tests, and there continues to be a paucity of developmentally appropriate biomarkers in pediatric medicine.

The US Children's Health Act of 2000 specifically authorized a national study involving biological components as measures of environmental and other influences. This Act paved the way for the National Children's Study, a longitudinal birth cohort study from 2008 to 2014 that did not progress beyond a pilot phase.[3] Despite some progress and critical recognition of the necessity for more inclusive pediatric biobanking studies, the closure of this study left a gap unfulfilled by the larger scientific community, with only 6% of biomarker publications on PubMed from 2012 to 2016 focused on pediatrics.[4] In other jurisdictions, fragmentation of the regulatory mechanisms that govern our biomedical research has led to a cottage industry of disconnected biobanks. In Australia where, despite many years of focused attention developing biobanking infrastructure, differences in state laws and regional policy confusion have prevented pediatric biobanks working together in a coordinated manner. This coordination is vital to maximize the research potential of its relatively small and broadly geographically distributed patient population. Despite attempts to form networks that indicate a united front,[5] the Australian pediatric biobanking community still lacks a common and universally applied standardized system for tissue handling for research between its centers and across different state lines. The consequences of this is that, in Australia, if an investigator needs to collect biospecimens, they set up their own collection strategy, call it a biobank just for personal purposes, because they are unable to rely on a wider biobanking infrastructure to support their research.

A quick fix is not on the horizon, with the notable absence of pediatric cohorts in the current All of Us Research Program (https://allofus.nih.gov/about/participation) and other large national projects suitable for establishing pediatric population-based normative values in molecular markers and functional assays over the course of child development. This is in the context of biospecimens from children being routinely collected, transiently stored, and likely discarded as part of regular clinical practice. Rather than being discarded, these biospecimens could be preserved and used for research purposes, provided such use achieves meaningful scientific advancement in support of generalized donor concepts of benefit.[6]

The degree to which existing pediatric samples will translate to new pediatric discoveries and clinical applications remains unclear, and in part attributable to the complex ethical concerns (ie, age of assent, reconsent, return of results) and operational challenges that may limit future and broad research. Furthermore, incorporation of biospecimen-enabled paradigms into emerging analytical platforms and associated complex data analytics is not yet standardized in order to inform common practices across collection strategies.[7] These challenges are well known in regard to cancer research and are likely even more prevalent in pediatrics, where tissue sample collections are limited to diagnostic purposes because

CHW	Children's Hospital at Westmead

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of their small individual volumes.[8] Without ample starting material, pediatric biobanking takes a lower priority over diagnostics.

To meet this challenge and realize a key opportunity for precision medicine, many institutions have independently implemented a solution in which biospecimens are systematically collected and stored from residual clinical material, or prospectively with informed consent under a research study targeting specific patient populations. However, solutions found in institutional biobanks remain at risk for falling short of the goal of facilitating diagnostic and prognostic discoveries that lead to future targeted and more highly risk-stratified therapeutic approaches. Remaining barriers include operational costs, optimal use of the biospecimen resource, and the quality and comprehensiveness of the clinical phenotypic data associated with the biospecimens. We describe the concept of the federated pediatric biocloud that unites independent retrospective and prospective models as a potential solution to the need for broadly accessible, well-governed, pediatric biospecimen banks paired with similarly high-quality phenotypic data and supported by data analytic tools. We propose an enhanced version of the federated biobanking model to include pediatric bioclouds, created at children's hospitals to function as precursors for individual biobanks before the formation of formal networks with the intent to network in the future. Borrowed from cloud computing concepts that link remote networks of computers to coordinate and manage a range of data, a biocloud, by definition, combines this element with the collection of biological samples under international best practice guidelines (recently updated by the International Society for Biological and Environmental Repositories[9]). As is the case with other research models, the merits of a federated pediatric biocloud model are best realized when used by an interdisciplinary research team that includes clinical and translational researchers and data scientists and methodologists.

Retrospective Biobanking: The Children's Hospital at Westmead (Sydney, Australia) Example

Retrospective biobanking is the practice of collecting, storing, and redistributing tissue biospecimens after they have been collected for clinical purpose. Generally, this is performed before specific research questions have been posed and requires the biobanking staff to work with established routine tissue handling practices such as those undertaken during the clinical management of patients by clinicians, surgeons, and pathologists. Biobanking embedded as a routine and generic practice within the patient management pathways of a hospital naturally creates a biocloud environment, building on systems already formed that are designed to manage biospecimens with direct linkage to patient clinical data. The Children's Hospital at Westmead (CHW) in Sydney, Australia has operated a tumor bank for the past 20 years and is a prime example of a successful retrospective biobank that has the goal of facilitating research into childhood cancer. CHW admits approximately 150 new oncology patients each year, which is considered a small patient population, requiring a common practice to approach each patient in the same manner to maximize the opportunity to build a meaningful collection for future unspecified research. This led to motivations by professionals who aimed to embed biobanking infrastructure within the hospital such that it operates alongside patient care pathways. Our retrospective biocloud was aimed to achieve 4 key elements: develop a simple plan that is easily integrated into routine hospital practice; address the project with the hospitals ethics committee and obtain generic clearance to practice as a service facility, not as a project per se; engage and involve all clinical staff at all levels through standardized practice; and build the required infrastructure that joins all aspects of the biocloud, including patient management, consenting, tissue handling, data linkage, and researcher engagement.

With this plan mapped out, the establishment of the tumor bank came about in 1998 with opportunity to leverage funds promised during a government political election campaign. Simple and natural arrangements were realized between the Children's Cancer Research Unit and the CHW Oncology and Pathology Departments that worked alongside patient care pathways. This process was overseen by an ethics committee endorsed tumor tank committee that has been in operation since the initiation of the study. Even in its early stages of development, the CHW tumor bank was to wake on a biocloud format, where the value of biospecimens would be defined by the detail of the provenance of the tissue collection and handling as well as the availability of annotated clinical and patient care data. Retrospective models of biobanking function by collecting all tissue that is residual to that required for diagnosis or clinical application. The CHW tumor bank makes such samples available to local, national, and international researchers through an open access policy, requiring an application and local review. In this manner, samples are not biobanked with specific projects in mind, nor are they linked to particular promises researchers may make to patients that certain questions will be studied. This approach allows the biobankers to use a common and generic consent form for each patient interaction, simplifying the message to a single narrative for all participants and in turn limiting the options to simple broad questions, providing clarity in knowing and respecting patient wishes. Because retrospective biobanks collect residual tissue from clinical samples, they do not request that patients go through additional biopsy procedures and instead seek permission for residual biospecimens to be managed by the biobank for future unspecified research. The request to patients and families is built on engendering their trust, first and foremost. This trust was not just around the biospecimen management, but also for the opportunity for the biobank to provide researchers with de-identified clinical data linked to the tissue sample, in essence, a biocloud.

The CHW tumor bank proactively reaches out to researchers exploring disease states that are of immediate

consequence to the hospital placing the biobanker as a driver of research in an active role that promotes their resources through push out biobanking.[10] As an active participant in research generation, a retrospective biobanker also acts as a gatekeeper for the resource, taking on a regulatory responsibility from within the hospital environment. By working in a generic hospital biocloud, the biobanker can annotate the biospecimens with clinical data captured during the patients' clinical management, enabling data linkage as well as value added tissue processing, clinical evaluation, interpretation through pathology review and patient engagement. Because this work is performed over an extended period of time, patients often have progressed to a final clinical outcome of interest, providing a richer set of clinical data, yet often from older treatment protocols. As such, this information may provide some limitations to the immediacy of clinical relevance to certain studies and needs to be borne in mind during experimental design.

For the CHW tumor bank, the value of its activity is seen in the research it has supported.[11-13] Childhood cancer is considered a rare disease, and therefore the ability for researchers to access sufficient numbers of tumor specimens to meet statistical power and produce meaningful findings is enabled by biobanks with consistent collection strategies as embedded practice. By having the biocloud relationships in place before the research questions are posed has considerable advantages for small centers. Generic bioclouds ensure rare samples collected over many years are sufficiently available to meet researchers' needs. Bioclouds that follow established best practices provide standardization of processes over extended periods of time, ensuring that biospecimens and annotated linked data are fit for purpose. Internally, hospitals that practice retrospective biobanking should create assurances between participating department, clinicians, and pathology staff about the requirements for sample provision to research and thereby generalizing how the ethical and privacy regulations are adhered too, thereby shortening time for project review and creating confidence in a process that everyone should follow. Ideally, retrospective biobanking provide a firm basis for policy setting by governing and management leaders.

Prospective Biobanking: The Johns Hopkins All Children's Hospital (St. Petersburg, FL) Example

Prospective biobanking can be defined as the collection of samples in response to particular research questions being posed. This process targets specific cohorts to investigations before an outcome of interest has occurred, establishing baseline information with subsequent follow-up over disease or developmental progression. Although these types of studies can be quite complex and expensive to set up, they present the best opportunities for interdisciplinary teams to frame optimal specimen and data collections within flexible recruitment strategies that are responsive to sample quality or diversity issues. In short, prospective biobanking forms specific bioclouds, where targeted samples are collected as they emerge and are identified as suitable for inclusion in particular studies, and clinical data are subsequently extracted to meet the study requirements as agreed upon and approved by the ethics approvals. Bioclouds of this nature, despite being formed with a specific question in mind, still benefit from uniform biobanking services that engage with other hospital departments to enable these research studies, by establishing common and standardized means for enabling the tissue based research to occur, meet regulatory compliance, and improve researcher productivity. Prospective biobanking however, is also more prone to sustainability and design challenges, as evidenced by the early closure of the National Children's Study. As such, feasibility analyses and institutional commitment to interdisciplinary support are critical.

In its simplest form, a prospective biobank requires both a protocol individualized to each cohort study and a specific informed consent appropriately describing the types of samples and data elements that will be collected in conjunction with any added risks or potential benefits. The use of the samples should be described, including the main aims of the study and plans for future research. An important consideration at larger research hospitals should include the potential for some study participants to be approached for multiple banking studies, wherein patients may experience consent fatigue if exposed to a barrage of participatory-related activities. Prospective studies can have considerable complexity in study implementation given the need for patient screening by specific inclusion and exclusion criteria, enrollment after informed consent discussion, and the collection of specific data elements across the initial and longitudinal follow-up visits. Sample collection requires a closely collaborative relationship between clinical research coordinators and the biobanking team to foster protocol adherence, research regulatory compliance, and biospecimen quality assurance, wherein a singular biocloud with harmonized collections may help with compliance and fatigue-related challenges.

Prospective research in an era of precision medicine demands optimal usage of limited funding in an ever-evolving landscape of complex ethical and scientific requirements. A new model for pediatric academic health centers has recently been described utilizing centralized and specialized research cores able to dynamically support all manner of clinical trials and translational research efforts, collectively integrated into an operational infrastructure designed to maximize efficiency, sustainability, and scientific reproducibility.[14] As part of this model, the Johns Hopkins All Children's Pediatric Biorepository was implemented in 2013 to support long-term strategic aims centered on improving clinical outcomes and children's health by leveraging multiple subspecialty areas of expertise in the collection, processing, storage, and distribution of biological samples and associated data. Fully integrated into the hospital environment using physical space adjacent to the Department of

Pathology and Laboratory Medicine, the Biorepository was established by applying well-validated sample management principles and biorepository best practices on a state-of-the-art platform envisioned by an interdisciplinary team. The Johns Hopkins All Children's Pediatric Biorepository serves as a unique prospective-focused template that other academic health systems may find useful as a model addressing critical aspects such as sustainability and governance. Now in its sixth year of existence, the Biorepository has successfully implemented 15 disease-specific cohort studies, as well a birth cohort study and a healthy "norms" study for the benefit of investigators institution-wide. This has resulted in collection of over 60 000 banked specimens for both protocol-specified and future as-yet unspecified uses.

The Johns Hopkins All Children's prospective banking approach has other distinctive benefits to the aforementioned real-time opportunities for realigning recruitment or trouble shooting sample collection quality issues. The majority of prospective studies have specific aims with detailed immediate uses for accrued samples, with additional samples partitioned and banked as aliquots for envisioned future use. Multiple aliquots serve a dual purpose, first by allowing for iterative testing (ie, a plasma sample can be analyzed for metabolomics and then proteomics), with each round of testing guiding the next. When combined with comprehensive genetic and transcriptome profiling, companion sample testing can be quite effective in pinpointing pathway associated disruptions and biological mechanisms not known before the start of the study. Subsequent samples can otherwise be used for multiplatform comparisons or identical testing to confirm the original results, a critical requirement for validation of any new biomarker. If identical samples are at hand, reproducibility efforts can be dramatically expedited by removing the need to enroll new participants. Second, the initial aims of any prospective study must be funded for a predetermined period of time to establish the bank. Subsequent use of other aliquots may then be used to share costs and sustain future banking, as well as serve as a preestablished source for future grant proposals in alignment with institutional goals.

Another major asset to pediatric prospective studies is participant engagement. The infrastructure required to screen, inform, and consent study participants presents opportunities to keep enrollees informed on study progress and on the use of their samples (including return of research results), as well as providing a mechanism to reconsent at each visit or after reaching the age of majority. Although reconsenting is not always required unless participants continue to interact with the study after turning 18, it offers an ethically preferable option for researchers wishing to maximize benefit to study participants and to satisfy participant wishes for decision making after transitioning to adulthood.[15] Engagement through reconsent is particularly important for participants whose parents' provided consent when they were at a very young age and remain unaware their samples persist in a biobank as a potential resource for research.[16]

Federated Pediatric Bioclouds

Federated biobanks are not a new model, arising in part from networking of existing biobanks because of translational researchers' needs for large numbers of samples unobtainable using localized banking methods.[17] It is surprising that, given the successes of these networks, in some cases arising from well-funded national initiatives, there is scarce representation, if not a complete absence, of federated pediatric-focused biobanks.[18,19] This issue likely stems more so from a lack of focus on the process of pediatric biobanking rather than the availability of samples themselves and serves as an important driver toward rethinking the concept for pediatric applications.

A reasonable solution to this biospecimen challenge requires the creation of interdisciplinary biorepositories built as centralized resources within the local children's hospital that integrate all facets of tissue handling for successful research and include appropriate linkages to phenotypic data before formal networks are constructed. Strategic relationships between medical, scientific, and administrative leaders are key to moving biobanks beyond a collection and storage initiative lacking manageable uniformity to a multipurpose infrastructure with broader goals of supporting institutional research priorities and unmet external needs (eg, federated networks, consortia, patient advocate–driven initiatives). Linked phenotype data should include common data elements available through the electronic medical record, specific research data, and clinically annotated datasets specific to broad and future use, of which the latter is often not available. A recently published dataset for brain cancer biobanking by the Brain Cancer Biobanking Australia provides an important example of what is needed across all pediatric specialities.[20] Such bioclouds should exist as a singular institutional resource that is responsive first to patient management (ie, clinical priorities, experimental trials), but also strikes a balance between appropriate institutional governance and investigator access.

Defining pediatric biocloud characteristics include the following: origination does not rely on but may be harmonized with existing and future federated networks; interdisciplinary focus to embed biospecimen best practices within clinically driven data and biospecimen repositories and clinical research studies; broadly consented sample access and requests for use monitored using a local governance structure; responsive to local, national, and international health disparities; community engagement; and active involvement in study surveillance and monitoring through study implementation, participant enrollment, and sample distribution.

When these collection strategies are harmonized across multiple centers and paired with electronic medical records and clinically driven informatics, key risks such as sustainability and biohoarding (the tendency for institutions and investigators to restrict access to their own biobanks[21]) can be mitigated, particularly in areas where more efficient sample management is an institutional necessity. Through the

increased use of pediatric bioclouds, an accelerated timeline from hypothesis to discovery can be achieved in child health and disease.

Within the pediatric clinical research domain, owing to the low numbers of patients with any particular disease, multicenter studies are often required to cover specific patient populations unlikely to be present in any time of federated biobank. In consequence, clinical trials, cohort studies, and collaborative research increasingly have built in to their consents and protocols biospecimen collection and banking, which is done for both protocol-specified aims and hypotheses, as well as for future as-yet unspecified research aims and hypotheses, often at great costs. With the increased demand and competition for biological samples from within our treating hospitals as well as from multicenter clinical trials requiring biospecimens be externally stored in large centralized biobanks, the value of efficient biocloud infrastructure within our local centers is vitally important to reduce costs and encourage productive research. It is paramount organizations involved with child health research improve the value of pediatric care by investing in proactive biospecimen approaches that will enable faster responses to emerging technologies and knowledge under the constraints of extramural underfunding.[22] In the current absence of such infrastructure, studies move forward using the only accessible samples which likely have unknown preanalytical variation and may not be well-suited to fulfilling the analytical aims or maximizing the future analytical potential of the proposed studies. This issue contributes to the lack of reproducibility in preclinical research, a problem estimated to amount to $28 billion in wasted costs in the US alone.[23] Commonality between standardized samples available through pediatric biocloud model will provide reassurance to basic and data scientists study designs that increase rigor in the research process and improve reproducibility.

Conclusion and Future Directions

Reliance on clinical archive samples simply as a product of the diagnostic process, although noteworthy for considerable progress in the past, is often insufficient to ensure meaningful research use in pediatrics, where samples are typically limited in both size and numbers, and where common data elements are often lacking. Ideally, sample banking protocols should be prospective in design and guided at the onset by biobankers, data scientists, and clinical experts; however, this model can be difficult to achieve based on available institutional infrastructure, expertise, and logistical considerations. This challenge can be met by strategically linking interdisciplinary efforts, such as the 2 models of biobanks presented here, into federated pediatric bioclouds that ensure specimen banking practices are intraoperable and interoperable within institutional priorities and consortia or government initiatives without compromising the best interests of patients, some of whom whose lasting legacy may exist only in the use of their banked samples in a representative biocloud.

The Childhood Cancer Survivorship, Treatment, Access and Research Act of 2018 provides encouragement this issue has broad recognition and a path forward. It is hoped that this type of legislation provides a template for biobanking efforts beyond cancer, which prioritizes sample collections driven by scientists, physicians, and patient advocates into the most effective use, rather than the most convenient. The existence of appropriately designed biobanks, whether retrospective or prospective, provides a means to augment decreased funding opportunities and unenticing profit margins that delay drug development for many pediatric issues characterized as rare diseases. The availability of fit-for-purpose samples has the potential to invigorate research and development in certain sectors, particularly if patient advocacy groups or foundations are appropriately engaged to empower bioclouds. This advantage is no doubt recognized by academics and health groups, because the proportion of children's hospitals with established biorepository infrastructure is increasing, highlighting the importance of early recognition and need to harmonize to fully leverage the power of networked bioclouds. ■

Author Disclosures

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