Clinical Center Pediatric Research Strategic Plan

October 2023

Executive Summary

Pediatric research is essential to understanding health and disease throughout the lifespan. Increased understanding of early life disease influences and trajectory could lead to potential interventions and improved health later in life. The National Institutes of Health (NIH) Clinical Center (CC) is the Nation's research hospital, offering hope for those unable to find a diagnosis or effective treatment elsewhere. Establishing strategic priorities in pediatric research at the National Institutes of Health (NIH) Clinical Center (CC) will guide expansion and ensure that NIH remains on the cutting edge of scientific discovery across the age spectrum. The CC is a unique clinical research environment, and strategic investment that leverages distinctive aspects of care and research within the CC will expand the impact of NIH's pediatric research. By capitalizing on an innovative and collaborative CC environment that enjoys flexibilities in study timelines, pediatric research could facilitate a meaningful return on investment for NIH in terms of impact on patient life expectancy and optimizing health as well as provide unique opportunities to train future child health researchers.

The NIH CC Pediatric Research Strategic Plan (PRSP) working group was charged with identifying scientific opportunities for pediatric research at the CC with the greatest potential for significant impact. The PRSP working group identified several scientific research priorities and also outlined cross-cutting infrastructure enhancements needed to make pediatric research at the NIH CC more efficient. Scientific priorities include:

- Expanding the scope of natural history studies to support research on the continuum from diagnosis to treatment throughout disease trajectory within the same disease
- Building a unified clinical and scientific infrastructure to support gene therapy, CAR-T, and other cell therapy studies
- Exploring the efficacy of precision medicine interventions in rare, non-malignant diseases
- Increasing the number of pharmacokinetic and pharmacodynamic studies to improve rational medication use and proper dosing in children
- Performing metabolic phenotyping across a variety of pediatric conditions, as well as linking metabolic phenotyping in nutrition studies and assessing the impact of diet on immune phenotypes and metabolism
- Developing a cohort of all pediatric patients at the CC to measure physical and mental health and disease across disorders, along with a deeply phenotyped pediatric cohort of healthy volunteer children to establish a standard set of control samples that can be used across studies
- Increasing support for research studies in pregnant and lactating people

Background

Pediatric research is vital to understanding health and behavior throughout the lifespan. Early life experiences and exposures influence health and disease, and interventions early in life could enhance health and reduce illness burden, particularly in later years. The NIH Clinical Center (CC) is at the forefront of discovery research to learn about the nature and course of diseases and to develop therapies to improve health outcomes. As the Nation's research hospital, the NIH CC is a House of Hope for many seeking diagnosis and treatment for complex, rare, or refractory diseases.

Today, the CC has approximately 1,600 active research protocols, 35 percent of which include children. Of those, about half are natural history studies and half are interventional trials of new therapies, including first-in-human or first-in-pediatrics studies. Overall, 15 NIH institutes have studies at the CC that include children. The multi-institute pediatric unit within the CC includes 18 beds, 11 day hospital stations, an inpatient behavioral health unit with six beds, and an outpatient clinic with 21 care rooms. Scientific and technologic advances are changing the face of NIH intramural pediatric clinical research. Researchers are investigating illnesses with increasing complexity and severity, and there is strong interest in providing interventions earlier in the lifespan. The number of credentialed pediatricians at the CC has also increased significantly in the past decade, reaching nearly 250 in 2022. The number of protocols including children has substantially increased in the past two decades.

Against this backdrop, the NIH Clinical Center (CC) Strategic Plan (*The NIH Clinical Center at 65: People, Places, Capabilities*) identifies child health research at the CC as an area for expansion, given the progress in diagnosis and treatment of pediatric disease as well as the increasing recognition of the impact of childhood health on health and disease later in life. To plan for the future of pediatric research at the CC, the Pediatric Research Strategic Plan (PRSP) working group was charged to:

Identify the most impactful scientific areas of pediatric research in which the NIH can play a major role to substantially improve child health. Using this horizon scanning, the group will perform long-term, strategic planning for intramural trans-NIH clinical pediatric research to occur over the next decade and beyond.

The PRSP working group identified research or research resources that the CC is uniquely positioned to conduct or create. For example, NIH is the world leader in rare disease research, and the CC is also home to unprecedented natural history studies that can follow patients for decades. This enables opportunities to diagnose and treat patients at younger ages, thereby avoiding many disease manifestations that develop over time, and also to follow pediatric patients into their adult years. The CC Pediatric Research Strategic

Plan can guide decisions related to recruitments and resources for the CC, as well as aid in identifying potential research partners.

The PRSP working group will present the Strategic Plan to the CC Governing Board for consideration. Although the group's charge did not extend to including cost considerations or specific infrastructure requirements for the proposed research agenda, they did consider the extent of investment required to implement the recommendations (see Table 1).

NIH CC Pediatric Research Strategic Plan (PRSP) Working Group

The PRSP working group was established following discussions with the CC Governing Board and the NIH-wide Pediatric Research Consortium (N-PeRC). It includes members from 13 NIH ICs (Appendix A), including ICs with the highest proportion of pediatric patients involved in research at the NIH CC. The group began meeting in Summer 2022. Four PRSP subgroups were created to discuss particular areas of research in greater depth: Natural History Studies, Gene Therapy, Innovative Research (other than gene therapy), and Resources.

To further inform their efforts, the PRSP working group developed a brief, two question survey for members of the Association of Medical School Pediatric Department Chairs (AMSPDC). The survey was distributed to all AMSPDC members to provide an opportunity to identify areas of research in which the NIH CC could have the greatest impact on child health, and potential resources that could be developed and made available to the research community that would be challenging to develop within an academic research institution. The survey received 15 responses. Ideas generated by respondents largely echoed those generated by the PRSP working group.

The PRSP working group also reached out to the Children's Inn at NIH to discuss how the visions for the future of pediatric research at the Clinical Center and the future of the Children's Inn could align and complement each other. The vision for the Children's Inn includes increased adaptability to serve all pediatric, teen, and young adult patients and their families, regardless of the severity of their condition. The Inn aims to align its services with NIH patient recruitment goals and to reduce challenges families encounter when participating in intramural research. These aims match well with PRSP working group efforts to consider expanding research to include younger patients and to increase adaptation of treatment protocols and spaces to be child-friendly.

The CC Pediatric Planning Group (PPG) set the stage for this strategic planning effort with their January 2022 report that focused on preparations to build capacity for increased numbers of pediatric patients and how to adapt emergency, intensive, and outpatient care

for the pediatric population at the CC. That group also assessed feasibility of reducing the lower age limit for admissions from currently three years to six months. Some of the PPG recommendations have been implemented (e.g., additional clinical providers in anesthesiology trained to care for pediatric patients) and others are under consideration.

Strategic Research Priorities

For decades, NIH research has enabled Americans to live longer, healthier lives. Learning more about disease courses and mechanisms in children and developing early life interventions allows the possibility to enhance health for a lifetime. The mission and infrastructure at the NIH CC provide an ideal environment to pursue several research priorities that will push the boundaries of pediatric research in the coming decade and beyond. Priorities identified by the PSRP include leveraging the robust natural history studies to extend research from diagnosis to treatment throughout the disease trajectory within the same disease; gene therapy trials; pharmacokinetic and pharmacodynamic studies of drugs in pediatric populations; nutrition, metabolic, and immunologic studies; creating deeply phenotyped comparison cohorts; and studies on pregnant and lactating people.

Natural History Studies: Moving from Diagnosis to Treatment

Among the major strengths of the NIH CC is that it allows clinical researchers the ability to initiate and sustain long-term natural history studies that are critical to understanding specific diseases and their outcomes. The depth and duration of information collected in natural history studies cannot be duplicated at any other research institution in the U.S. These studies are also vital to developing therapies and targeted treatments under new FDA guidelines defining the role of natural history studies in regulatory considerations for rare diseases. The PSRP identified **supporting research along the continuum from diagnosis to treatment throughout disease trajectory within the same disease** as a priority for pediatric research at the CC. Creating more opportunities to move from diagnosis to treatment capitalizes on resources within the CC and helps shift the culture to helping children *through* research instead of protecting them *from* it. The extramural Undiagnosed Diseases Network and the Rare Diseases Clinical Research Network, including the initial Undiagnosed Diseases Program in the intramural program, may be among the ideal partners for studies moving from diagnosis to treatment, given the program's experience with bedside to bench to bedside studies. In addition, developing registries for a variety of diseases will capture longitudinal information on chronic diseases. These data can be used to track disease progression, identify potential biomarkers and outcome measures, inform clinical trial design, and serve as external control for regulatory submissions of new therapies.

Developing Pediatric Therapies and Therapeutics

Gene therapy and related precision treatment approaches offer the possibility of life-altering treatment for patients that could reduce or even eliminate the need for ongoing treatments. The CC PRSP working group identified developing new therapies and therapeutics for children as a top priority. This includes gene therapy (including gene editing), CAR-T and other cellular therapies, molecularly targeted therapies, non-invasive neurostimulation therapies, behavioral interventions, prevention strategies, pharmacokinetic and pharmacogenomic studies in children, and developing pediatric medical devices.

Gene Therapy and Direct Molecular Therapeutics

The NIH CC is ideally suited to develop specialized resources necessary for gene therapy trials in children as well as to conduct those cutting-edge trials. **Building a unified clinical and scientific infrastructure to support gene therapy that could be used to develop treatment options for many single gene disorders in children could create significant advances in biomedical research and improve quality of life and outcomes.** This investment would include infrastructure for protocol development, delivery, monitoring, and outcome measurement, as well as scientific development such as specific delivery platforms (CRISPR, vector-based, mRNA, etc.) and reagents that would allow investigators to develop and optimize a therapy for any gene of interest. Some of these therapies may result in the greatest benefit when given early in life to very young patients. Expanding the ability to care for children less than three years old in the CC would greatly benefit this effort. Collaboration with industry partners and the Foundation for NIH could also accelerate the development and testing of new gene therapies.

Precision Medicine Interventions for Rare, Non-Malignant Diseases

The NIH is at the forefront in the discovery of novel genetic and rare, complex acquired disorders of childhood. For several of these diseases, the NIH CC has the largest cohort of such patients worldwide. Leveraging detailed characterization of the pathophysiology of these diseases by NIH investigators, this offers the opportunity to **explore the safety and efficacy of novel targeted therapies in patients with such rare disorders** and to promote potential collaboration with industry. In addition, learning about rare diseases opens the door to understanding mechanisms in more common diseases.

Pharmacokinetics, Pharmacodynamics, Pharmacogenomics

A major gap in pediatric care is lack of information on how children's bodies are affected by various medications – even some common medicines have not been thoroughly tested in children. The PRSP working group identified pharmacokinetic, pharmacodynamic, and pharmacogenomic studies in children as a strategic research priority. The CC should

increase the number of these studies in children to better understand pharmacokinetics and metabolism of drugs in diverse pediatric populations. This may include collaboration with industry partners and regulatory agencies to ensure that drugs are appropriately tested and labeled for use in children. The CC has a pharmacokinetic unit with experienced research staff that could collaborate on these studies. Thus, this priority would require less initial financial investment and could operationalize quickly.

Nutrition and Metabolic Studies

The CC is well positioned to allow longer term feeding and energy expenditure studies in children to assess nutrition and metabolism. **Comprehensive metabolic phenotyping across a variety of pediatric conditions, as well as nutrition studies that could be linked to the metabolic phenotyping,** would be valuable to the research community and are unlikely to be conducted by other research entities.

Collaboration with the new NIH Center for Immunology, Inflammation and Autoimmunity (CHI) will enable **assessment of the impacts of different diets on immune phenotypes and metabolism**. CHI aims to provide a unique NIH-wide resource to develop novel technologies for translation of human immunological-mediated disease and pathophysiology into clinical applications. CHI provides investigators with access to integrated activities and diverse support for items such as: technology innovation/enhancement; multi-omics and biobanking; high-dimensional immune phenotyping; biomedical computational analysis; single cell sequencing; systems immunology, and proteomics and analytical technologies.

Deeply Phenotyped Cohorts

The PRSP working group also identified valuable research resources that could be uniquely suited to the capabilities of the CC. One such resource would be to **develop a deeply phenotyped pediatric-specific healthy control cohort** with data and biospecimens that would be made widely accessible to the entire pediatric research community. Data collection could include multi-omics, deep metabolic and immunophenotyping, genome-wide sequencing and epigenetics, sleep studies, and biospecimens as well as cognitive and socio-emotional data. The goal of such a resource is to establish a standard set of control samples and pediatric reference data that can be used across studies, which will reduce variability and increase reliability of results.

This effort will be complemented by plans for the *All of Us* Research Program to deeply phenotype participants whose genomes are sequenced as part of that program and who have clinically significant variants identified or variants in genes in which nothing is known about the associated phenotype. The *All of Us* Program plans to begin enrolling children in 2024, and the deep phenotyping programs could be developed and expanded collaboratively. Additionally, the CC could serve as a resource to deeply phenotype

asymptomatic infants who have undergone newborn sequencing as part of extramural research initiatives such as BabySeq.

A second **cohort study could be designed to include all pediatric patients at the CC to capture measures of pediatric health and disease across multiple disorders**. This approach will enable researchers to study broad pediatric populations and identify commonalities across different diseases.

Research at the Earliest Age: Pregnant and Postpartum People

CC **support for research in pregnant and lactating people** will help to address a crucial research gap to understand the effects of disease and medication on pregnant and lactating people. These studies could include examining conditions in the fetal, perinatal, and neonatal period, including clinical observations, imaging studies, and multi-omics, among others. The natural history studies at the CC could also provide opportunities to observe outcomes in pregnant patients with rare diseases. The CC could also design comprehensive studies of postpartum depression, a leading cause of maternal mortality, and potential treatments.

Lactation studies are also vital, given that so few medications are labeled for use by lactating people. These studies include **pharmacokinetic and pharmacodynamic tests that could lead to medication label changes as well as metabolic profiles to better understand the composition of human milk.** Many of these studies could be low risk and feasible in very young children. These studies could also be operationalized with lower initial investment costs. The CC currently owns some capital equipment necessary to conduct lactation studies and additional infrastructure investment may be minimal.

Cross-Cutting Priority: Infrastructure Investment to Accelerate Research Discoveries and Enhance Data Sharing

Crucial first steps to enhance and expand pediatric research at the CC include infrastructure investments that will remove barriers to establishing and conducting observational and interventional research studies and will facilitate data harmonization and sharing. In some cases, reorganizing the infrastructure and centralizing efforts could make pediatric research at the CC more efficient. Many of these infrastructure enhancements could occur with minimal additional financial resources. Workforce training opportunities will provide opportunities to enhance collaboration across the scientific focus areas of CC pediatricians. Additional infrastructure investment will be needed to support the scientific priorities identified by the PRSP working group.

Pediatric Core for Protocol Development

Establishing a core focused on protocol development for pediatric clinical research studies would benefit all ICs. While some ICs have protocol development resources, a central resource specializing in pediatric studies at the CC would streamline this time-consuming process for investigators and reduce duplication of effort. This core could also work to develop standardized protocols that can be used by all ICs that would promote consistency and facilitate data comparison across studies. For example, generating modular case report forms (CRFs) to use across clinical trials will aide protocol development and future data integration, and the use of pediatric common data elements (CDEs) will expand research opportunities and facilitate secondary data analyses. Creating these tools and resources will enhance NIH-wide collaboration among CC researchers as well as speed up time from concept to trial completion.

A pediatric protocol development core could also house **a pediatric natural history concierge team to offer guidance on best practices in natural history studies** and to facilitate optimized data collection enabling shared data elements and databases across studies (e.g., creating common templates and variables). For gene therapy and other cellular therapy studies, cross-institute resources for protocol and investigational new drug (IND) development as well as study sponsorship and database would reduce burden on individual investigator efforts and accelerate the clinical trials timeline.

Creating some common protocols and having a central resource would also facilitate an opportunity to align with the NIH-wide Digital Strategic Plan (*Digital NIH: Innovation, Technology, and Computation for the Future of NIH*), which includes a critical cross-cutting capability to develop a common architecture with well-defined standards to enable data integration. Relatedly, the PRSP recommends **adding a pediatric section to the CC Institutional Review Board for developmentally appropriate** review of all pediatric, adolescent, and young adult protocols at the CC. This section (or another section) should also include expertise in evaluating protocols for research studies with pregnant and lactating people.

Enhancing Infrastructure to Support Scientific Research Priorities

New imaging resources and training will be necessary to conduct state of the art research in pediatric and pregnant populations. Equipment for infant and young child imaging may include ultrasound or MRI examinations for fetal imaging and increased capability in neuroimaging to better understand the developing brain. Imaging facilities will also need adaptation to include child-friendly components. For example, increased use of a mock scanner for behavioral preparation would enable more successful participation and potentially less medical sedation with imaging protocols, and opportunities for

patients to watch movies or listen to music during scans would improve the experience. Developing standard protocols for pediatrics, including consideration of aspects such as fasting or preparation for imaging studies, will be essential, along with staff who are comfortable with pediatric patients and pediatric dosing. Opportunities for interventional radiology and other cutting edge treatments involving imaging (e.g., high-intensity focused ultrasound to move treatments across the blood-brain barrier) would be ideally suited to research at the CC.

In addition to specialized imaging resources, the scientific priorities identified by the PRSP working group will require infrastructure investment to varying degrees. Investment in personnel, lab facilities, and specialized equipment will be needed. For example, infant-sized pods would be necessary for metabolic phenotyping for the youngest patients, and special laboratories would be needed to produce gene therapy products.

Some of the scientific priorities may also require additional consideration for ethical, legal, and social implications. For example, gene therapy trials in pediatric populations at the CC will necessitate a continued focus on safety and regulatory issues, including establishing procedures to evaluate the risk-benefit for the specific gene platform and plans for anticipated risks based on target organ systems.

Workforce Training

The number of pediatricians at the CC has increased over time (currently numbering more than 250), and in 2022, the CC established the Department of Pediatrics and Pediatric Hospital Medicine Service. The vision for the Department of Pediatrics is to enable groundbreaking pediatric studies through collaborative networks by providing compassionate, age-appropriate, high-quality care. The top priority for the newly created Department is to create a model of care for pediatric inpatients that functions across institutes.

Adding training opportunities for pediatricians at the CC will increase collaboration and competency. For example, Pediatric Grand Rounds or walk rounds would help pediatricians better understand the scope of pediatric research in the CC. Similarly, a directory or catalog of all pediatric research being conducted at the CC would be a useful resource, not only to promote collaboration at NIH, but also to recruit future investigators and train future academic leaders in child health research. Leaders and supervisors should also explore meaningful recognition and reward for providing compassionate, high-quality pediatric care at the CC.

Conclusions

The NIH CC is the nation's largest hospital devoted entirely to clinical research. As such, the CC is uniquely poised for paradigm-shifting breakthroughs in pediatric research. As the

CC looks to the future, the PRSP working group identified several high-priority research areas to consider for investment in the next decade and beyond. Gene therapy and other cellular therapies top the list of recommendations for investment in innovative research with high potential to enhance children's lives. The CC also presents an excellent opportunity to study pharmacokinetics and pharmacogenomics of medication in children and in pregnant and lactating people. This would require little new financial investment and would address a significant gap. Natural history studies and rare disease research are cornerstones of research at the CC, and they will be integral to research moving forward. Underpinning all of these possibilities for the future are ideas for infrastructure development that will facilitate collaboration and advance scientific discovery at the CC and beyond. Many of the infrastructure developments suggested by the PSRP would not require extensive investment and could be initial action items for implementation. Given the growth of pediatric research at the NIH CC over time and the scientific opportunities on the horizon, renewed and expanded focus on pediatric research should be prioritized among all CC research activities.

Although the PRSP's charge did not include consideration of costs or resource requirements, the group recognizes that some of the strategic research priorities may be implemented in the near term while others are longer term goals. Table 1 identifies priorities that may be effectively cost-free, have comparatively low to moderate costs, or requires substantial investment.

Table 1. Relative Financial Investment Needed to Implement CC Pediatric Research Strategic Plan Priorities

Relative Financial Investment	Strategic Plan Priority
Minimal	Add a specific pediatric component to the IRB
	Develop a directory of CC pediatric researchers
	Establish Grand Rounds focused on child health
Low/Moderate	Pediatric pharmacokinetic and pharmacodynamic (PK/PD) studies
	Lactation studies (including PK/PD)
	Infant/pediatric metabolic studies
	Phenotyping pediatric *All of Us* participants that are identified as having genomic variants
	Core for pediatric protocol development
	Unified clinical research form
	Developing pediatric common data elements
	Pediatric-friendly imaging/scanning protocols and facilities
	Establish a natural history study concierge
Major	Gene therapy studies
	Deeply phenotyped pediatric-specific healthy control cohort
	Cohort study including all CC pediatric patients at the CC across multiple disorders

The CC will also evaluate potential partnerships with local or regional pediatric facilities for safety, transfer, protocol integrity, and joint protocol development to enable pediatric trials. The aspect of partnerships was beyond the current scope of this working group but can be further explored in relation to each scientific priority as they are further developed. The research priorities identified in this strategic plan represent the working group's current thoughts on facilitating and conducting innovative science. The priorities may shift over time as the pace and nature of science change, though the need for research involving individuals of all ages will remain.

Appendix A: NIH Clinical Center Pediatric Research Strategic Plan Working Group Members

Chairs

Diana W. Bianchi, MD
Director
NICHD

Brigitte Widemann, MD
Chief, Pediatric Oncology Branch
NCI

Melissa Parisi, MD, PhD
Chief, Intellectual & Developmental Disabilities Branch
NICHD

Ben Solomon, MD
Clinical Director
NHGRI

Members

Rebecca Brown, MD, MHSc
Lasker Clinical Research Scholar
NIDDK

Jim Gilman, MD
CEO
Clinical Center

John Glod, MD, PhD
Clinical Director, Pediatric Oncology Branch
NCI

Adam Hartman, MD
Program Director, Division of Clinical Research
NINDS

Beth Kozel, MD, PhD
Lasker Clinical Research Scholar
NHLBI

Maryland Pao, MD
Clinical & Deputy Scientific Director
NIMH

Debara Tucci, MD, MS, MBA
Director
NIDCD

Lisa Rider, MD
Head and Senior Clinician, Environmental Autoimmunity Group Clinical Research Branch
NIEHS

Luigi Notarangelo, MD
Chief, Laboratory of Clinical Immunology and Microbiology and Chief, Immune Deficiency Genetics Section
NIAID

Michael Ombrello, MD
Chief, Translational Genetics and Genomics Unit, Pediatric Research Branch
NIAMS

P.J. Brooks, PhD
Acting Director, Office of Rare Disease Research
NCATS