Eunice Kennedy Shriver National Institute of Child Health and Human Development

Healthy pregnancies. Healthy children. Healthy and optimal lives.

National Advisory Child Health and Human Development (NACHHD) Council

Meeting Summary

6710B Rockledge Drive, Rooms 1425 and 1427,
and virtually
Bethesda, MD
June 9-10, 2025

U.S. Department of Health and Human Services (HHS)

National Institutes of Health (NIH)

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

The NACHHD Council convened its 188th meeting at 12:15 p.m.[1] Eastern Time on Monday, June 9, 2025, at 6710 Rockledge Drive, rooms 1425 and 1427, in Bethesda Maryland. This hybrid meeting was open to the public from 12:00 p.m. to 5:00 p.m. The Council reconvened Tuesday, June 10, 2025, from 8:30 a.m. to 12:05 p.m. for a session that was closed to the public. As provided in Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S.C., and Section 10(d) of Public Law 92-463, sessions for review, discussion, and evaluation of grant applications and related information are closed to the public. NICHD Acting Director Alison Cernich, Ph.D., presided.

Council Members Present[2]

Alison Cernich, Ph.D. (Chair)
Anna Aizer, Ph.D., M.S.
Susan L. Brooks, J.D.
Marcelle Ivonne Cedars, M.D.
Danien Fair, Ph.D.
Cynthia Gyamfi-Bannerman, M.D.
Ethylin Wang Jabs, M.D.
Yvonne A. Maldonado, M.D.
Ignatia Van den Veyver, M.D.

Council Members Absent

None

Ex Officio Members

Patricia Dorn, Ph.D.
Gayle Vaday, Ph.D. (Department of Defense)
Reem Ghandour, DrPH, MPA (Health Resources and Services Administration)
Jose L. Contreras-Vidal, Ph.D. (National Advisory Board on Medical Rehabilitation Research Council Liaison)

Executive Secretary

Rebekah Rasooly, Ph.D.

In each section of this meeting summary, the number in parentheses following each heading refers to the time stamp on either the Day 1 NIH Video Cast or the Day 2 Transcript.

[1] The meeting was originally scheduled to begin at 12:00 p.m. but was slightly delayed due to technical difficulties.
[2] Council members recuse themselves from the meeting when the Council discusses applications from their own institutions or when a conflict of interest may occur. This procedure applies only to individual applications discussed, not to en bloc actions.

I. Call to Order and Introductory Remarks (0:03)

Dr. Cernich opened the meeting and welcomed the members of the NACHHD Council and all in-person and online attendees.

Review of Confidentiality and Conflicts of Interest (2:00)

Rebekah Rasooly, Ph.D., the Council's executive secretary, expressed appreciation for the Videocast and Information Technology staff who quickly solved the technical difficulties that delayed the opening of the meeting. Dr. Rasooly reminded NACHHD Council members that they are required to read, agree to, and sign the confidentiality and nondisclosure rules for special government employees on the Council member website before evaluating any NIH grant applications. Before the meeting, Council members received and signed the required conflict of interest certification forms. Dr. Rasooly also reminded council members that they are required to recuse themselves and leave the meeting before any discussion that involves organizations or universities for which they are in conflict, in addition to those listed in the Council action document. Finally, Dr. Rasooly stated that Council members are not allowed to serve on any NIH peer review panel while serving as Council members, because NIH policy states that individuals may not serve on both the first and second levels of review.

Council Minutes (3:10)

Dr. Ceders made a motion to approve the January 2025 NACHHD Council meeting minutes as written. Dr. Aizer seconded the motion. Council voted to approve the minutes.

Future Meeting Dates (6:40)

Dr. Rasooly announced that the future Council meeting dates are scheduled for September 8-9, 2025 (NIH Bethesda Campus, Building 45); January 26-27, 2026 (virtual); June 8-9, 2026 (6710B Rockledge Drive); and September 1-2, 2026 (NIH Bethesda campus, Building 45).

II. NICHD Director's Report (5:50)

Dr. Cernich introduced herself and stated that she was asked to serve as Acting Director of NICHD in April. She thanked Dr. Diana W. Bianchi for her service as Director of NICHD.

NICHD Strategic Plan and Recent Initiatives (6:21)

In her Director's Report, Dr. Cernich highlighted the release of the NICHD 2025 Strategic Plan, which was a "refresh" and update of the 2020 strategic plan. The overall thematic areas of the 2025 plan were similar to those included in the 2020 plan, although many of the specific objectives and some of the aspirational goals were updated to reflect the progress of science since 2020. Dr. Cernich thanked the NICHD staff for their efforts and Council members for their feedback. Dr. Cernich pointed out the 2024 Research Highlights report, available on the Council website.

Dr. Cernich described the NICHD Data and Specimen Hub (DASH), a centralized resource that allows researchers to share and access de-identified data from studies funded by NICHD. More than 230 studies on over 60 topics are included in DASH. Dr. Cernich explained that DASH is being migrated to an NIH-supported data repository platform that will provide better security and additional functionality for users. All data in DASH will be made available. DASH data will be unavailable during the period of migration, which began May 5, 2025. Data are anticipated to be available again in the fall of 2025.

Dr. Cernich described the new NIH-wide Autism Data Science Initiative (OTA-25-006). The strategic aims include (a) creating integrated data resources leveraging existing data, with appropriate privacy protections; (b) identifying and addressing research gaps via targeted data generation; (c) supporting analysis of integrated data resources that link genetic and non-genetic risk factors; and (d) providing a venue for replication of analyses. This is intended to be a complementary initiative to "real world data platform" efforts being developed at HHS. Up to $5M per 2-to-3-year project period is anticipated. The application due date is June 27, 2025.

Dr. Cernich informed the Council that NICHD was asked to fund a National Academies study on current NIH pediatric research portfolio and structure. She stated that there is currently open a call for perspectives and comments – one for pediatric patients and families, which closes June 30, and another for pediatric health researchers, which closes July 1. The report is expected to be released in early 2026.

HHS and NIH Leadership Changes and Priorities (14:01)

Dr. Cernich reported that on February 13, 2025, the President established the Make America Healthy Again commission and requested an assessment to address childhood chronic disease. A report on behalf of the commission, released on May 22, 2025. Focused on four areas: (1) poor diet; (2) exposure to environmental chemicals; (3) lack of physical activity and chronic stress; and (4) "overmedicalization". Research suggested included long-term nutrition trials, lifestyle interventions, and precision toxicology. These efforts are expected to be ongoing.

A new "Operation Stork Speed" initiative, primarily led by FDA, is underway. The purpose of this project is to ensure the safety, reliability, and nutritional adequacy of infant formula. A Request for Information (RFI) on infant formula nutrient requirements has been published. Comments are due September 11, 2025.

Recent changes in NIH leadership include the appointment of Dr. Jay Bhattacharya as NIH Director. Dr. Matt Memoli, who served as Acting Director, will serve as NIH Principal Deputy Director. New Acting Directors at the IC level include: Dr. Courtney Aklin (NINR), Dr. Andrea Beckel-Mitchener (NIMH), Dr. Alison Cernich (NICHD), Dr. Carolyn Hutter (NHGRI), Dr. Jeff Taubenberger (NIAID), and Dr. Monica Webb Hooper (NIMHD). Within the NIH Office of the Director, Dr. Nicole Kleinstreuer will be acting as DPCPSI Director and Dr. Jon Lorsch, who is also the NIGMS Director, will be serving as acting OER Director.

Dr. Bhattacharya has stated priorities in the following areas:

- Improving Population Health, with an emphasis on chronic diseases;
- Reproducibility and Rigor;
- Innovation and Collaboration;
- Research Safety and Transparency; and
- Academic Freedom.

NICHD Budget and Challenges (17:09)

Dr. Cernich stated that NICHD's plan is to obligate all appropriated funds in FY 2025. The FY 2026 "skinny budget" includes a $18B cut to NIH and a consolidation of ICs to 8, plus the elimination of FIC, NIMHD, NINR, and NCCIH. NICHD would be consolidated with NIDCD in this budget.

The NIH Congressional Justification suggests using multi-year funding (multiple years of a grant award provided in one year) to a greater extent within Research Project Grants. The advantage of multi-year funding is that it provides more flexibility in the outyears; the disadvantages are that it is expensive in the initial year and limits total awards in that year. Dr. Cernich pointed out that multi-year funding is not "no year" funding, where those funds are available to be spent over multiple years and can be rescinded at a later time. In response to a question from Dr. Ceders about the potential impact of multiyear funding, Dr. Cernich stated that the proposed appropriations levels are proposed, not actual levels. However, even without a budget cut, an increase in multi-year funding will result in a reduction in the number of new awards. Dr. Jabs asked whether no-cost extensions can be granted in the case of multi-year/up-front funding. Dr. Cernich clarified that there are additional restrictions on no-cost extensions at the end of the project period when upfront

funding is used. In addition, phased awards are also an option. The exact impact on any given award will depend on the project period, grant mechanism, and other factors. Dr. Dorn asked for clarification about the use of multi-year funds. Dr. Vaday noted that the Department of Defense grant programs that she administers use multi-year funding to ensure that the entire project will be supported regardless of future budget years.

In response to a question from Dr. Jabs, Dr. Cernich stated that there is a proposal to reduce the indirect cost rate to 15%. However, Dr. Cernich added that as she understands it, this would require Congressional action.

Dr. Cernich stated that over the past several months NICHD lost staff in key functional areas through a directed reduction in force, incentives to leave the workforce, and loss of probationary employees. Other challenges include pauses in acquisitions, travel, communications, and meetings. Councils and scientific review were also paused, but are now resuming. There is a directed reduction in the number of funding opportunity announcements, although this is not affecting concept clearances that will be presented at this council. There have been also award holds and terminations. In response to questions from Dr. Aizer and Dr. Maldonado, Dr. Cernich stated that NICHD has not at this time been given additional specific guidance about high priority or low priority topics. NICHD has not been asked to alter the scientific content of the major themes of its research strategy. Dr. Cernich affirmed that NICHD is committed to advancing the progress of science within the agency mission to the full extent of the funding provided to support it.

Dr. Cernich reported that a temporary pause for paying foreign subawards was established, and additional justification was requested for foreign grant applications, while NIH finalizes a new award structure (see NIH guide notice NOT-OD-25-104). In the future, under a new NIH policy and system that are being developed, foreign components are expected to be allowed but will be treated as linked awards. This will facilitate tracking and monitoring of foreign subawards. It is hoped that this new process and systems to support it will be available in the fall. In the interim, NIH will not issue foreign subawards; will not accept requests to add a new foreign component or subaward to an ongoing project; renegotiate awards to remove subawards, allowing for rebudgeting when the work can be performed domestically and negotiate bilateral terminations if the project is no longer viable without the subaward.

NIH has prioritized the development and expansion of use for non-animal models. There is an intent to establish a new Office of Research Innovation, Validation, and Application within the NIH Office of the Director. This new effort will coordinate NIH wide efforts to develop, validate, and scale use of non-animal approaches. Such approaches may include organoids, tissue chips, or other in vitro systems; computational models; and real-world data applications. Dr. Cernich stated that this is not an effort to eliminate animal models, but

instead to increase use of non-animal approaches. Dr. Contreras-Vidal asked if additional details were available. Dr. Cernich stated that the initiative is now just taking shape, and more details are expected to be coming in the fall.

Dr. Cernich highlighted new policies to extend opportunities for early career researchers. NIH has granted automatic extension of early stage investigator (ESI) eligibility for one, two, or three recipient cycles. In addition, individuals with K awards who ended prematurely after January 1, 2025 will be eligible to apply for additional K awards. Multiple Council members expressed concerns about losing young scientists as success rate decline with decreases in the number of awards from multi-year funding.

III. NIH CIT and OCIO: Enabling Access and Innovation with Advanced Technology (50:09)

Dr. Rasooly introduced Dr. Sean Mooney, director of the NIH Center of Information Technology (CIT). Prior to joining CIT, Dr. Mooney served in a number of positions, most recently as Professor of Biomedical Informatics and Medical Education and Chief Research Information Officer at the University of Washington School of Medicine. Dr. Mooney also served as the Associate Director of the National Alzheimer's Coordinating Center.

NIH IT Infrastructure (51:01)

Dr. Mooney stated that NICHD has been a leader in data science, data sharing, and technology to support the future of research. He stated that CIT has partnered across the NIH to build and revise technology to create an ecosystem of cybertechnology to enable scientific progress. Dr. Mooney stressed that the science must define what technologies are needed to support the work.

Dr. Mooney described computing at NIH as being centered first on people. Many people at the NIH are needed to develop and implement the technology that supports the NIH mission. Enterprise infrastructure includes the "boring things" – email, Teams, data centers – that scientists need to use every day. The federal government has moved to investing more heavily in the cloud to achieve a digital ecosystem. Data platforms and analytics and artificial intelligence build on this ecosystem to serve both the scientific and administrative needs of the NIH.

Dr. Mooney explained that he oversees the Office of the Chief Information Officer, which focuses on IT strategy, enterprise architecture, IT governance, and information security. In his role as CIT Director, Dr. Mooney directs CIT's provision of enterprise IT back to the NIH. He described CIT as the operational arm of the NIH for technology, including collaboration, research computing, networks, and other operations.

Partnerships among CIT, the NIH Office of Data Science Strategy, the National Library of Medicine, and the NIH ICs have led to a series of successes in the IT arena. These successes illustrate the size and scope of the NIH IT infrastructure. Specific achievements include:

- Establishing the NIH network, which securely and reliably connects over 45,000 people in 200 NIH buildings through 4,300 miles of network cabling so that scientists and administrative staff can do their jobs effectively each day;
- Supporting NIH collaborations, including over 2.5 million virtual meetings hosted annually in Zoom and Teams, over 1 billion emails sent and received, and over 1 million gigabytes of data in SharePoint and OneDrive at the NIH; and
- Making performance computing services available, via BioWulf, for the intramural program. This service is very popular, Dr. Mooney reported, and is currently operating at full capacity.

Cloud and Data Infrastructure (57:16)

NIH has invested in the cloud and data infrastructure through the STRIDES initiative, aligned with NIH's strategic plan for data science. Dr. Mooney stated that the use of the cloud allows NIH to pursue modern, integrated, intuitive, efficient, and secure data-driven technology. It generates cost savings and efficiencies for the research community through economies of scale and greater discounts. Strong partnerships from cloud providers such as AWS, Google Cloud, and Microsoft Azure allow NIH to adopt the latest and greatest technologies. Dr. Mooney stated that every type of data that you can imagine is available within STRIDES, including over 365 petabytes of data, 802 million computational hours, over 2,700 accounts, and over 5,000 people trained. STRIDES has accounted for an estimated $126M in cost savings compared with non-cloud data options. Many programs are supported – including NICHD-related programs such as Gabriella Miller Kids First. The NIH Cloud Lab, within STRIDES, allows any NIH investigator to get access to specific training about how to develop and use cloud-based tools.

Artificial intelligence (AI) and Cloud Data Platforms (1:09)

Standard platforms and cloud data repositories can help enable AI and related technologies. The investments NIH makes in AI and related technologies continued to grow over the past several years, more than tripling between 2019 and 2023. As AI funding has expanded, the types of activities used have diversified.

Standard cloud data platforms can help researchers process, store, and share data. CIT is trying to help to make these platforms more interoperable. More

enterprise thinking for these standards is needed to make data and access easier and more impactful. A good example of such a standards-based approach is the NIH Researcher Authentication Service, or RAS, which has been a collaboration among CIT and data science and sharing offices at the NICHD, IC, and OD levels. RAS has enabled researchers to save time and money using a common toolkit for logging in and accessing resources. Dr. Mooney specifically called out NICHD for its partnership in implementing RAS. Another set of tools that are under development are workspaces--cloud-based analytical environments where researchers can bring together tools and data for analysis. These workspaces allow scientists to combine data from multiple repositories. The hope is that the future, NIH will have a "plug and play" architecture that will make connections between repositories and workspaces faster, standardized, and more secure.

There are many (at least 77) standardized AI use cases at NIH, according to Dr. Mooney, and AI is being integrated into NIH operations without the need for data scientists. Such use cases include

- helping researchers match patients to clinical trials;
- message management and document production;
- interactive chatbots; and
- classify data management and sharing plans.

AI can provide efficiency gains, but Dr. Mooney acknowledged that use of AI can also be inequitable and raise safety, privacy, and ethical concerns.

Biomedical cyberinfrastructure can bring the power of advanced IT to solve research problems. Building new tools, and ensuring interoperability, will help create a "technical garden" at the NIH. Within the NIH, there is a need to improve clinical trials technology, support technology careers, and enable enterprise cloud systems. In a broader focus on biomedical research, NIH can convene and lead the community, help improve technological fluency, and provide products and services to support an ecosystem that takes advantage of the cloud and core research facilities. Dr. Mooney encouraged participants to look for the CIT newsletter and once again thanked NICHD for its partnership.

IV. Bioinformatics and Pediatrics Research (1:21)

Dr. Cernich introduced Dr. Kenneth Mandl. Dr. Mandl is the Director of Computational Health Informatics at Boston Children's Hospital and is also the Donald A.B. Lindberg Professor of Pediatrics and Biomedical Informatics at Harvard Medical School. He is also the co-chair of the National Academy of Medicine's Digital Health Action Collaborative.

Dr. Mandl stated that for pediatric research, diagnostic use cases within pediatrics can illustrate how to bring bioinformatics to pediatric research. He related how his son had both colitis and a seizure disorder as a young child,

and when Dr. Mandl inquired about whether the seizures and colitis could be related he was told unequivocally no. Dr. Mandl and a postdoc fellow looked into large databases to investigate relationships between seizures and all autoimmune conditions, and they found that these autoimmune conditions were statistically associated with seizures. Dr. Mandl stated that large-scale data analysis can reveal patterns and relationships that are not observable by clinicians at the level of individual patients.

Dr. Mandl reported that a 2016 publication documented a Google AI procedure to diagnose diabetic retinopathy from retinal scans and photographs of the retina. The AI out-performed the clinicians in making the diagnosis. With inexpensive computational tools and storage, new means of multimodal data capture, AI, and cloud computing, new advances are possible in pediatrics. However, it is important to make sure that we have the full context to assess prior probability. Dr. Mandl asserted that the concept of prior probability is not well handled in our health care system. Many times, the information needed to determine prior probability is not available in medical databases. For example, there was a study of hypertrophic cardiomyopathy in NEJM that showed that genetic variants assumed to be absolutely related to the condition were normal in black patients although not in white patients. In one study of strep throat, Mandl and team assessed the true probability of a positive strep test and adjusted for the proportion of positive tests in the local area. The adjustment greatly improved the probability of a correct diagnosis. Dr. Mandl advocates using large databases to improve diagnoses in this way as a matter of routine.

According to Dr. Mandl, it is difficult to get the data in the right place at the right time. Data needs to be shared more widely. The promotion of the use of electronic medical records and growth of application programming interfaces (APIs) can enable data connections and sharing that would not be possible otherwise. This can also help clinicians from different medical specialties to have access to tailored views of the electronic medical record so they each have the information they need. Were this practice to be expanded, patients also could have access to their own data, including the clinician notes, and create a uniform medical record for themselves. Sharing such records with responsible AI applications could then accelerate diagnostic improvements, research (NIH), post-market surveillance (FDA), and public health (CDC). Dr. Mandl reported that he had met with HHS officials, and HHS officials are interested and planning to use these APIs to move health data around the system. However, regulating interoperability of electronic health records--rather than regulating user interfaces and other aspects--may be necessary.

A network of 6 children's hospitals is using a federated network where each institution keeps their own data locally, and processes data via AI locally, but queries can be made to share data in standardized formats across the network. Common approaches to consent, data storage, representation of genomic data,

are needed to make this work. Dr. Mandl stated that this standardization made it possible to identify patients with a rare disease for clinical trials. In addition, clinicians and researchers are looking across the network at patients who are seeking diagnosis for rare pulmonary diseases. This may facilitate conferences of clinicians to direct the next set of treatment approaches.

Dr. Cernich shared that NICHD has worked on these issues with Patient Centered Outcomes Research Institute (PCORI) and the HHS Office of the National Cccordinator (ONC). She suggested that information on related activities be shared. Dr. Maldonado asked about data security issues associated with these projects. Dr. Mandl said that once data are shared from the care delivery system to apps, terms of service govern the use of the data and it is under the purview of the FTC. In Apple's health app, a patient can download a standardized copy of their data, patient privacy and control is put first. Apple has taken a strong stance on privacy and patient control; when patients download their information to their phone, Apple cannot access or see the data unless the patient decides to share it, for example with a research study. In Mandl's federated data sharing networks, population level data are liberally shared as aggregate counts only. More processes are required when line level data are shared. For driving forward a national scale data infrastructure, in Dr. Mandl's opinion, the technology is not the limiting factor, but governing how the data are most safely and effectively used is where important attention is needed.

V. Immune Dysregulation in Down Syndrome: Mechanisms and Clinical Trials (1:54)

Dr. Cernich introduced Dr. Joaquin Espinosa. Dr. Espinosa is the Executive Director at the Linda Crnic Institute for Down Syndrome at the University of Colorado and Professor of Pharmacology at the University of Colorado School of Medicine and holds the Anna and John J. Sie Endowed Chair in Genomics.

Dr. Espinosa began by describing people with Down syndrome as "a diverse population that are surpassing all expectations". He pointed out that people with Down syndrome are living longer than ever before and accomplishing impressive feats. Dr. Espinosa emphasized that Down syndrome is not rare. The birth rate has not decreased and with large gains in life expectancy, there are more people with Down syndrome alive than ever before. A newborn born with Down syndrome today can expect to live to 60 years.

The cause of Down syndrome – an extra copy of chromosome 21 – has been known since the late 1950s. Chromosome 21 was sequenced in 2000, leading to the identification of approximately 225 genes. This chromosomal abnormality is not a mutation, but simply 1.5 times the gene dosage. However,

although the cause of Down syndrome is known, it is not clear how the hallmark characteristics of Down syndrome result from the trisomy.

It has become clear that people with Down syndrome have a distinct clinical profile compared to individuals without Down syndrome. There are a series of traits that are common, although variable, in individuals with Down syndrome. These include neurodevelopmental delay, stunted growth, early aging, and craniofacial features. Individuals with Down syndrome have a reduced risk of many cancers, atherosclerosis, hypertension, and allergies. Individuals with Down syndrome have an increased risk of Alzheimer's disease, congenital heart disease, autoimmune conditions, lung infections, and vision and hearing conditions. In addition, their risks for autism spectrum disorders, seizure disorders, and other conditions also exceed that of the general population. To help people with Down syndrome lead longer and healthier lives, it will be necessary to study the co-occurring conditions.

In 2017, a productive collaboration between self-advocates, members of Congress, the Global Down Syndrome Foundation, and NIH led to the development of the INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE) project. A substantial increase in NIH funding for Down syndrome occurred. The 3 components of the INCLUDE program are (1) basic science, (2) cohort development, and (3) clinical trials. For example, an early INCLUDE-supported basic science project showed that trisomy 21 activates the interferon response. This finding led scientists, including Dr. Espinosa, to explore the role of the immune response in skin conditions among people with Down syndrome. Clinical trials for immunotherapy among people with Down syndrome and skin conditions are ongoing. Moreover, Dr. Espinosa reported that this line of research also led to studies focused on therapies for Down syndrome Regression Disorder (DSRD).

A large cohort study supported by the INCLUDE project, known as the Human Trisome Project, provides -omics data and biospecimens from thousands of participants, and these data are shared through the INCLUDE data hub. Dr. Espinosa stated that one key observation from the cohort study is that about 75 percent of adults with Down syndrome have been diagnosed with at least one autoimmune condition. Over half of people with Down syndrome have autoimmune thyroid disease (either hypothyroid or hyperthyroid), over a third have one or more autoimmune skin conditions, about 10 percent have celiac disease, and other autoimmune conditions – type I diabetes, psoriasis, and others – are also more prevalent among people with Down syndrome compared with the general population. Over 80 percent of these co-occurring autoimmune conditions are diagnosed during childhood.

Research supported by INCLUDE showed that people with trisomy 21 had an over-active interferon response. Dr. Espinosa stated that this is consistent with previous and ongoing research that demonstrated interferon hyperactivity

in mouse models of Down syndrome. In the interferon response, cytokines activate different types of immune cells; an overactive interferon response is a known risk factor for autoimmunity. Many pathogenic cytokines are highly elevated in people with Down syndrome. This takes place because there are 4 interferon receptors encoded on chromosome 21. The inflammation observed in the blood of people with Down syndrome is similar to that observed in people fighting a severe COVID infection. It is hard to find an aspect of the immune system that is not dysregulated in adults with Down syndrome. This helps explain why people with Down syndrome are susceptible to lung infections.

A hyperactive immune response may also help explain other features of Down syndrome. For example, a plasma metabolomics analysis revealed widespread metabolic dysregulation in people with Down syndrome. They displayed activation of the kynurenine pathway, which produces neurotoxic metabolites involved in many neurological conditions, including seizures. Researchers wondered what would happen if they could normalize copy numbers just for the receptors. Using CRISPR, the scientists deleted one copy in a mouse model. This resulted in the normalization of the receptor expression, although the genes were not changed. A key conclusion of this paper is that the interferonopathy in Down syndrome starts in the prenatal period. Medicines known as JAK inhibitors are available, and these small molecules are designed to inhibit the JAK enzymes that are acting downstream of the interferon receptors. The action of these JAK inhibitors is fully reversible, as they clear from the body relatively quickly. A phase II open label clinical trial of JAK inhibitors focuses on whether they can help people with Down syndrome who have serious autoimmune skin conditions. Key end points include safety, interferon scores, cytokine scores, skin pathology, and cognition. The safety endpoint was met, with the safety profile similar to that observed in the general population. The JAK inhibitor reduced interferon activity to the range for the general population, but no lower. Examples of effectiveness were observed in patients with alopecia and psoriasis. Most cognitive tests showed gains, but there was no placebo control so the results were hard to interpret. In one case report, however, there were significant gains in a young women with Down syndrome regression disorder. This raises the question about whether Down syndrome regression disorder may also be an autoimmune condition.

A new clinical trial is recruiting now to repurpose benzodiazepine, IV immunoglobulin, and JAK inhibitors for individuals with Down syndrome regression disorder. All three of these medications are FDA approved for other conditions, and now will be tested in a Phase II, three arm, open label trial. The idea is to arrive at a personalized medicine approach to the treatment of Down syndrome regression disorder.

Dr. Cernich congratulated Dr. Espinosa on a clear and compelling presentation showing the effectiveness of the INCLUDE program. Dr. Jabs asked if there was an age-dependent effect within the clinical trial results. Dr. Espinosa

stated that there was not such an effect, at least not in the usual way that might have been expected. However, what has been observed is that the effectiveness of the medications on skin conditions appears to be higher if the treatment is started earlier.

VI. Voice of the Participant (2:23)

Dr. Cernich introduced Ms. Angela Lombardo, who is a parent of Mr. Isaiah Lombardo, an individual with Down syndrome who has been affected by skin conditions. Ms. Linda Roan is a Community Liaison with the Linda Crnic Center for Down Syndrome at the University of Colorado. She is attending today as a parent of an adult daughter who has had Down syndrome regression disorder and has benefitted from being a participant in research trials.

Ms. Lombardo described Mr. Lombardo's medical history, including not only Down syndrome but co-occurring conditions, including Hirschsprung disease, cardiovascular complications, and a variety of skin conditions. Mr. Lombardo has been employed and participated in many activities, but the skin conditions and subsequent lesions and abscesses have had a major negative impact on his quality of life and he has needed multiple surgeries. Despite many consultations with dermatologists and trying many medications and over-the-counter remedies, the conditions continued to get worse.

Ms. Lombardo described her experience with the research studies at the University of Colorado as "amazing". She stated that the research team worked very well with Isaiah. The effects of the treatment have been transformative. At one point Mr. Lombardo had to discontinue the medication for three months because of health insurance issues, and the serious skin issues recurred almost immediately. Once the medication resumed, the beneficial effects also resumed. Ms. Lombardo stated that the positive effects on his psychological and physical health have been dramatic.

Mr. Lombardo expressed his appreciation for being able to participate in the study. He credits the impact of the trial with helping him to be able to work, connect with friends, and participate in activities. He stated that the treatment has saved him a great deal of pain. Mr. Lombardo said that he especially appreciated the research team's interaction with him. They explained everything to him, and talked with him primarily, rather than just speaking to his mother. This made him feel seen and heard.

Ms. Roan described the impact of the INCLUDE project on her daughter and her entire family. Ms. Roan's daughter Miah experienced Down syndrome regression disorder. At 18, around 2014, Miah travelled to a college program for people with disabilities. When she came home for Thanksgiving, she had

been engaging in odd, difficult, and repetitive behaviors. She did get better for about 6 months, but then regressed again to the point where she could not even say her name or feed herself. In 2016 Miah's medical team tried electroconvulsive therapy (ECT) and this appeared to work, but several years later Miah regressed again and she was entirely unresponsive to treatment (including ECT). After several years, Miah tried an immunotherapy and although it did not work, it led to a collaboration among physicians. Miah became a participant in the clinical trial conducted at the University of Colorado. Miah's brain was greatly helped, and her skin conditions improved. She is now doing well, working and interacting with friends, after several years of treatment. Ms. Roan showed a short video to show Miah's behavior pre-and post-regression. She expressed her thanks for the clinical trials and their positive effect on her daughter.

Dr. Van den Veyver asked the participants what advice they would give to researchers. Ms. Roan said her advice would be to stick with it. Ms. Lombardo stressed the importance of breaking down barriers to clinical research. She reiterated that she would not have been able to have her family participate in the trials without having the travel costs reimbursed, for example.

VII. Concept Clearances (2:52)

Dr. Rasooly reminded the attendees that concept clearances represent early planning stages for funding initiatives such as requests for applications and contract solicitations. Experts in the field must approve concepts before they can be developed into formal initiatives. Concepts are not always developed into initiatives, and the details on an initiative often differ substantially from the original concept.

Dr. Antonello Pileggi from the NICHD's Obstetric and Pediatric Pharmacology and Therapeutics Branch presented a concept entitled the "National Pediatric Medical Device Ecosystem". He stated that medical technologies and new medical devices are growing in number and types of indications for adults, but for pediatric indications, these figures have remained relatively static. Pediatric device development is perceived as a high-risk endeavor with low and highly uncertain return. Innovation is hindered by lack of infrastructure specifically for pediatric devices. The concept under consideration would address this lack of infrastructure to promote the development and availability of safe and effective pediatric medical devices to improve health outcomes. The initiative aligns with NICHD strategic plan, the NIH mission, and the Administration's priorities. Dr. Gyamfi-Bannerman asked if there was a potential role to develop devices for use in pregnancy. Dr. Pileggi said this specific concept was focused on pedatric indications. There is value in extending the research area into pregnancy, although they are out of the scope of this concept. Dr. Cernich pointed out that existing work in the portfolio includes devices for use in

pregnancy, but consideration of the pregnancy period would be helpful. Dr. Gyamfi-Bannerman moved to approve the concept, Dr. Van den Veyver seconded. All council members voted in favor of approval.

Dr. Karen Winer from the Pediatric Growth and Nutrition Branch presented the concept for the "Pediatric Scientist Development Program (PSDP)". Dr. Winer stated that the PSDP was a longstanding NICHD career development program that was designed to provide a bridge between formal research training and beginning a career as an independent scientist. The PSDP prepares pediatric scientists with the scientific knowledge, state of the art training, and mentoring needed to compete for NIH grants in the current highly competitive environment. This program provides pediatricians with this experience during their late pediatric residency and subspecialty fellowship training. Over the 5 years the PSDP has seen a two-fold increase in scholar applications. Since its inception, the PSDP has supported 235 research scholars. The majority of scholars have become NIH funded PIs, with 90 percent remaining in academic medicine, and many going on to hold distinguished leadership positions. Dr. Maldonado asked how this concept is coming about given that the previous PSDP grant was terminated. Dr. Rasooly and Dr. Cernich stated that to recompete the program, perhaps in a slightly different fashion, there should be a valid concept clearance. Dr. Van den Veyver suggested incorporating additional emphasis on data science. Dr. Cernich noted this suggestion. Dr. Aizer asked if there are areas of the country that are underserved and if so, would this program address that. Dr. Winer replied that the program is designed so that any interested scholar can apply, and it is not limited to individuals whose academic center received direct support from the grant. She also clarified that although the PSDP has historically emphasized basic sciences, other types of science are also included. Council voted to approve this concept.

Dr. Sonia Lee from the Maternal and Pediatric Infectious Disease Branch presented the concept for "HIV Pediatric, Adolescent, and Maternal Clinical Trials". A specific clinical trials network is needed to specifically address the needs of pediatric, adolescent, and maternal populations. Notable accomplishments under previous iterations of the program include reduction in vertical transmission of HIV; approval of medicines to treat children and adolescents; and approval of pre-infection prophylaxis in adolescents. This network will continue to collaborate with other HIV networks funded by the NIH. The initiative aligns with NICHD strategic plan, the NIH mission, and the priorities of the NIH Office of AIDS Research. Dr. Maldonado asked if the network would have global research included, and Dr. Lee responded that it would. Dr. Maldonado moved to approve the concept, Dr. Gyamfi-Bannerman seconded, and Council voted to approve the concept.

Dr. Virginia Salo from the Child Development and Behavior Branch presented the concept for "Impact of Technology and Digital Media Exposure and Usage

on Child and Adolescent Development". Dr. Salo stated that technology and digital media have become an integral part of daily life, with children having a high level of exposure. There is an urgent need to better understand the impact of technology and digital media exposure on child development and family interaction. Previous research under this initiative has been helpful. The initiative aligns with NICHD strategic plan and the NIH mission. The proposed concept would extend knowledge in this area, be broadly inclusive of NICHD populations, and emphasize transdisciplinary and cross-cutting research. Dr. Van den Veyver moved to approve the concept, Dr. Damien Fair seconded, and the Council voted to approve the concept.

Dr. Jiaqi O'Reilly from the Intellectual and Developmental Disabilities Branch presented on ClinGen Genomic Curation Expert Panels. This initiative will support manual curation of review and define clinical relevance of variations for the NHGRI program ClinGen. Expert panels use the ClinGen structure to link genomics to diseases. NICHD seeks to continue its leadership in this area related to NICHD priority topics and populations. The overall return on this investment has been high; more than 800 genes and over 3800 variations have been curated through this program thus far. Dr. Maldonado moved to approve the concept and Dr. Gyamfi-Bannerman seconded. The Council approved the concept.

VIII. Statement of Understanding (3:20)

The Statement of Understanding is a document that describes the Council procedures. The Statement has been updated for this year to reflect an NIH policy change that expands the NIH definition of a foreign applicant. This is not related to changes in how foreign applications are tracked. Dr. Jabs asked if the change was an NIH-wide policy. Dr. Rasooly indicated that it is an NIH-wide policy, and the Statement of Understanding simply reflects the policy change. Dr. Maldonado asked how joint appointments with foreign institutions are treated under the new policy. Dr. Rasooly replied that the institution as listed on the application would be controlling in that case. Dr. Van den Veyver moved to approve, and Dr. Gyamfi-Bannerman seconded. The Council voted to approve the revisions to the Statement of Understanding.

IX. Closing Remarks (3:34)

Dr. Cernich stated that this was the conclusion of Dr. Contreras-Vidal's service to the Council as liaison to the NCMRR Board and thanked him for his service. She thanked all participants and ended the meeting.

X. Closed Session (June 10, 2025)

The meeting was closed to the public in accordance with the provisions set forth in Section 55f2b(c)(4) and 552b(c)(6), title 5, U.S.C., and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2). NACHHD Council members provided second level review of NICHD extramural applications.

XI. Review of Applications

The session included a discussion of procedures and policies regarding voting and confidentiality of application materials, committee discussions, and recommendations. Members absented themselves from the meeting during discussion of and voting on applications from their own institutions or other applications in which there was a potential conflict of interest, real or apparent. Members were asked to sign a statement to this effect. The Council considered and approved 773 NICHD-primary applications requesting $302,928,477 in direct costs and $423,169,132 in total costs.

XII. Adjournment

There being no further business, Dr. Cernich adjourned the meeting. The next Council meeting is scheduled for September 9-10, 2025, at the NIH Bethesda Campus, Building 45.

I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.[3]

Alison N. Cernich -S

Digitally signed by Alison N. Cernich -S
Date: 2025.08.22 09:30:18 -04'00'

Alison Cernich, Ph.D.
NACHHD Chair
NICHD Acting Director

[3] These iminutes will be formally considered by the Council at its next meeting. Any corrections or notations will be incorporated into the minutes of that meeting.

Rebekah S. Rasooly -S

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Date: 2025.08.21 14:45:51 -04'00'

Rebekah S. Rasooly, Ph.D.
NACHHD Executive Secretary
Director, NICHD Division of Extramural Activities