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National Institutes of Health

Twenty-second Meeting of the Clinical Center Research Hospital Board

October 21, 2022

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*absent

Executive Summary

The Clinical Center Research Hospital Board (CCRHB) of the National Institutes of Health (NIH) convened its 22nd meeting via videoconference on October 21, 2022. The meeting was webcast live and open to the public. A video recording is available online.

Norvell V. Coots, M.D., President and Chief Executive Officer (CEO) of Holy Cross Health, and Chair of the CCRHB, called the meeting to order at 9:00 a.m. ET and noted that this was his first meeting as Chair. Dr. Coots welcomed new Board members and noted the absence of Regina S. Cunningham, Ph.D., RN, FAAN, CEO of the Hospital of the University of Pennsylvania Health System.

Lawrence A. Tabak, D.D.S., Ph.D., Performing the Duties of the Director, NIH and Executive Director of the CCRHB, welcomed Dr. Coots as the new CCRHB Chair and the newly confirmed CCRHB members: David M. Baum, PMP, patient and member of the Clinical Center (CC) Patient Advisory Group (PAG); David C. Chin, M.D., M.B.A., Distinguished Scholar at the Department of Health Policy and Management at Johns Hopkins Bloomberg School of Public Health and School of Medicine; Dr. Cunningham; Antoinette Royster, patient and member of the CC PAG; and Craig E. Samitt, M.D., M.B.A., the founder and CEO of ITO Advisors. He also recognized the departure of the last founding member of the CCRHB, Richard P. Shannon, M.D., Chief Quality Officer at Duke Health, and thanked him for his service to the Board and NIH. Dr. Tabak reviewed current changes to NIH leadership, with several notable retirements and appointments.

Dr. Tabak presented an update on NIH's activities related to diversity, equity, inclusion, and accessibility (DEIA). NIH has developed an overall framework for the DEIA Strategic Plan and held many stakeholder and town hall meetings to learn how NIH can enhance its DEIA efforts. There was a strong consensus that NIH needs to be transparent about its workplace demographics. These data indicate that Hispanic or Latino representation at NIH is lower than national levels, and there is lower representation of individuals who are Black or African American; Hispanic or Latino representation is low in all job categories compared with the national representation. Dr. Tabak also highlighted the Power of an Inclusive Workplace Recognition Project, which is part of the UNITE initiative and showcases diverse members of NIH in portraiture across campus.

Dr. Tabak also shared two different funding initiatives. NIH recently awarded its first round of funding for the Faculty Institutional Recruitment for Sustainable Transformation (FIRST) program, which is focused on hiring critical masses of early-career faculty who have demonstrated commitment to inclusive excellence. Additionally, since 2015, NIH has committed to increasing support for early-stage investigators (ESIs). The original goal was to fund at least 1,100 ESIs per year, and in 2022, NIH funded 1,589 ESI applicants. NIH plans to continue to support ESIs through commitments from Institute and Center (IC) directors and funding investigators at overlooked or underfunded institutions, such as historically Black colleges and universities (HBCUs), Hispanic-serving institutions (HSIs), Tribal colleges and universities (TCUs), and institutions in rural areas.

James Gilman, M.D., CEO, NIH CC, welcomed the new CCRHB members and Dr. Coots as the newly appointed Chair. He also recognized Dr. Shannon and thanked him for his service to the CCRHB. Dr. Gilman gave an update on the ongoing searches to fill five leadership positions at the CC, including two recent vacancies at the Department of Transfusion Medicine and Hospital Epidemiology Service. Dr. Gilman also recognized upcoming award ceremonies where CC staff will be recognized, including the 2022 Clinical Recognition and CC Administrator of the Year Program, the 2022 NIH Director's Awards, and the CC CEO Awards.

Dr. Gilman said that the average daily census (ADC) numbers remain lower than before the pandemic; however, outpatient clinical visits have increased by 15%, and the number of new patients is up almost 10%.

Although the Centers for Disease Control and Prevention (CDC) changed their universal masking recommendations in health care settings, the CC has not changed its masking policy.

Dr. Gilman also provided an overview of the workflow for how the CC coordinates clinical research efforts and ensures patient safety.

CC leadership is also working to define the future of work and find the best way to get employees back to work in person at the CC. While staff members have shown they can work in a virtual setting, the communication and collaboration between patient care teams that occurs organically in person is lacking. The CC will find a solution to slowly begin bringing people back to work in person.

The quarterly report of patient and staff safety metrics, previously presented at Board meetings by David Lang, M.D., M.P.H., Chief, CC Office of Patient Safety and Clinical Quality (OPSCQ), will now be made available to the Board prior to each meeting and posted online for public viewing after each meeting.

John I. Gallin, M.D., Chief Scientific Officer and Scientific Director at the CC, as well as NIH Associate Director for Clinical Research, presented a historical overview of the CC and notable achievements and contributions to medicine that have come from CC research, particularly in the areas of cancer, transfusion medicine, hematology and sickle cell anemia, heart disease, infectious diseases, mental illness, endocrinology, and techniques and devices.

George Santangelo, Ph.D., the Director of the Office of Portfolio Analysis (OPA) at NIH, presented a summary on the use of artificial intelligence (AI) to analyze NIH Clinical Center research at scale from 2017–2020.

Cynthia Tifft, M.D., Ph.D., the Deputy Clinical Director and Senior Clinician of the Medical Genetics Branch at the National Human Genome Research Institute (NHGRI), and Patricia Todd, DNP, RN, APRN, PCNS-BC, CPEN, a Pediatric Clinical Nurse Specialist, Critical Care and Sedation Services within the CC Nursing Department, presented details on a pediatric research project at the CC and how the CC prepared to support these patients. Dr. Tifft provided an overview of GM1 gangliosidosis, a lysosomal storage disorder (LSD) that is particularly severe in infant populations. Dr. Tifft's team recently launched a gene therapy trial in infant and juvenile GM1 gangliosidosis patients, which required planning on how best to support these small young patients. Dr. Todd described the steps that CC staff took to prepare for these infant patients, starting with a failure mode and effects analysis (FMEA) that identified gaps in the

CC's current capabilities. The team then filled in the gaps related to equipment and emergency response needed to support infant patients. The team also found gaps in competencies at CC and found specialists from Children's National Health System to provide support. Finally, there was a major effort to educate and train any CC staff that may work with these infant patients. The training involved classes, integrated in-lab simulations with CC providers, and in situ multidisciplinary simulations with Children's National Hospital providers. These efforts have allowed the CC to rethink its practices and move toward better support of younger and smaller patients.

Dr. Gilman said that based on these efforts to support the infants enrolled in the GM1 gangliosidosis gene therapy trial, the CC decided to assess whether it could reproduce this process and support similar pediatric research trials. The CC established the Pediatric Planning Group (PPG), which focused on pediatric emergency management, pediatric critical care, and pediatric subspecialty coverage. In February 2022, the PPG report was presented to the CC Governing Board, who requested an external review by pediatric thought leaders, leading to the development of the CCRHB Pediatrics Working Group (WG). The CCRHB Pediatrics WG is chaired by Sherin U. Devaskar, M.D., Executive Chair of the Department of Pediatrics at the University of California, Los Angeles (UCLA), Physician-in-Chief at Mattel Children's Hospital, and Assistant Vice Chancellor at Children's Health at UCLA Health. The CCRHB Pediatrics WG will review the PPG report and provide recommendations about whether the CC can successfully and safely conduct pediatric research. The WG plans to present their findings to the CCRHB in February.

Dr. Gilman requested a vote from the CCRHB to approve the CCRHB Pediatrics WG's charter and plans to present a report to the Board in February. The motion was unanimously approved. Dr. Coots expressed his excitement at reviewing the WG's findings at a future CCRHB meeting.

Meeting Summary
Friday, October 21, 2022

Welcome and Board Chair's Overview

Norvell V. Coots, M.D., President and Chief Executive Officer (CEO), Holy Cross Health and Chair, National Institutes of Health (NIH) Clinical Center Research Hospital Board (CCRHB)

Dr. Coots called the meeting to order at 9:00 a.m. ET, noting that this was his first meeting as Chair. He welcomed all the Board members, including those at various stages of the nomination process, as well as NIH leadership, the NIH community, and members of the public.

Dr. Coots noted that Regina S. Cunningham, Ph.D., RN, FAAN, was absent.

NIH Director's Remarks

Lawrence A. Tabak, D.D.S., Ph.D., Performing the Duties of the Director, NIH, and Executive Director, CCRHB

CCRHB and NIH Leadership Changes

Dr. Tabak said that he was delighted to introduce Dr. Coots as the new CCRHB Chair. This is a transitional meeting, with CCRHB members coming and going. He recognized the departure of the CCRHB's final founding member, Richard P. Shannon, M.D., and thanked him for all he has done for the CCRHB and NIH. There are several new board members: David M. Baum, PMP; David Chin, M.D., M.B.A.; Regina S. Cunningham, Ph.D., RN, FAAN; Antoinette Royster; and Craig Samitt, M.D., M.B.A. Dr. Tabak expressed his gratitude for the time and service of these new CCRHB members.

Dr. Tabak reviewed other departures and appointments among NIH leadership.

- James M. Anderson M.D., Ph.D., the Director of the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) for more than a decade, has retired. DPCPSI is within the Office of the Director and is the division head for many offices that coordinate activities across the agency (e.g., Office of AIDS Research, Office of Research on Women's Health). Bob Eisinger, Ph.D., will be serving as the Acting Director of DPCPSI. Dr. Eisinger has had a distinguished career at NIH and spent some time at DPCPSI, so it is exciting to have him in this acting role.
- Norman E. Sharpless, M.D., retired as the Director of the National Cancer Institute (NCI). Dr. Sharpless was actively involved in all CCRHB activities and will be greatly missed. President Biden recently appointed Monica Bertagnolli, M.D., as the Director of NCI. She is already deeply engaged with all NCI-related activities and the President's Cancer Moonshot℠.
- Anthony S. Fauci, M.D., the Director of the National Institute of Allergy and Infectious Diseases (NIAID), will retire at the end of 2022. Dr. Fauci has been Director of NIAID for 38 years and has worked at NIH for more than 50 years. His pending departure will mark an extraordinary change for NIH and the whole government.

- Andrea Norris, M.B.A., who is the NIH Chief Information Officer and the Director of the Center for Information Technology (CIT), recently announced her intent to retire at the end of the year. Ms. Norris oversaw the maturation and evolution of the CIT into a state-of-the-art, innovative research information technology network and will be greatly missed. One of her important achievements was helping researchers gain access to the cloud environment through the Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability (STRIDES) Initiative.
- Kevin Williams, J.D., was recently appointed the Director of the Office of Equity, Diversity, and Inclusion. Mr. Williams has already begun to make his mark, and NIH leadership is looking forward to working with him to instill diversity, equity, inclusion, and accessibility (DEIA) throughout the agency.
- Nina Schor, M.D., Ph.D., was recently appointed the Acting Deputy Director for Intramural Research (DDIR), following the departure of Michael Gottesman, M.D. Before assuming this role, she was the Deputy Director and the Acting Scientific Director for the National Institute of Neurological Disorders and Stroke and served as the Chair of the Department of Pediatrics at the University of Rochester. She brings a wealth of experience to her new role.
- Renee Wegrzyn, Ph.D., was recently appointed the inaugural Director of the Advanced Research Projects Agency for Health (ARPA-H) by President Biden. Dr. Wegrzyn has been able to get to work right away thanks to the foundational work done by Acting Principal Deputy Director of NIH Tara Schwetz, Ph.D. Dr. Wegrzyn will now be able to create the scientific agenda for ARPA-H, and NIH looks forward to working with her.
- President Biden also appointed Arati Prabhakar, Ph.D., as the new Director of the Office of Science and Technology Policy. Dr. Prabhakar will serve as the Chief Science Advisor to the President. Francis Collins, M.D., Ph.D., will finish his service as the Acting Chief Science Advisor to the President, but he remains at the White House on a part-time basis, working on special projects for the administration.

Awards

Dr. Tabak shared notable honors received by NIH staff and awardees.

- Carolyn R. Bertozzi, Ph.D., and K. Barry Sharpless, Ph.D., are NIH-funded researchers who received the Nobel Prize in Chemistry for their work related to click chemistry. Dr. Bertozzi used click chemistry to identify carbohydrate-decorated structures within physiological systems. Dr. Tabak has personally collaborated with Dr. Bertozzi on several projects, so it was gratifying to see a collaborator win this prestigious prize.
- The winners of the 2022 Albert Lasker Basic Medical Research Award were NIH-funded researchers Richard O. Hynes, Ph.D.; Erkki Ruoslahti, M.D., Ph.D.; and Timothy A. Springer, Ph.D.
- H. Clifford Lane, M.D., won the 2022 Paul A. Volcker Career Achievement Service Medal from the Partnership for Public Service. Dr. Tabak commented that he could not think of a more deserving winner for this award. Dr. Lane is a consummate public servant

who has played an enormous role in the nation's response to many infectious disease crises, including Ebola and human immunodeficiency virus (HIV).

- Four member of the NIH staff were recently named new members of the National Academy of Medicine: Carlos Blanco M.D., Ph.D., from the National Institute on Drug Abuse; Eugene V. Koonin, Ph.D., from the National Center for Biotechnology Information and the National Library of Medicine; Bruce J. Tromberg, Ph.D., who is the Director of the National Institute of Biomedical Imaging and Bioengineering; and Jennifer Webster-Cyriaque, D.D.S., Ph.D., who is the Deputy Director of the National Institute of Dental and Craniofacial Research.

DEIA Activities

With the help of many people, NIH has developed an overall DEIA Strategic Plan Framework. The three core principles of this framework are to implement organization practices to center and prioritize DEIA in the workforce, grow and sustain DEIA through structure and cultural change, and advance DEIA through research.

NIH has held many stakeholder and town hall meetings, and there has been a strong consensus that NIH needs to be transparent about its workplace demographics. Dr. Tabak shared NIH workforce data on race/ethnicity, sex, and disability status from the fourth quarter of fiscal year (FY) 2021 and said that NIH plans to provide quarterly updates on these demographics. Although Hispanic or Latino representation is lower than those groups' national representation, the overall demographic data indicate that the demographics of NIH are similar to national demographic data; however, these data do not tell the whole story.

The NIH workforce demographic data were stratified by job category: scientific occupations, health and research occupations, and infrastructure occupations. In the scientific occupations category, there is lower representation of individuals who are Black or African American and Hispanic or Latino. Hispanic and Latino representation is low in all job categories relative to the national representation. By making these data transparent and available, the goal is to raise awareness of NIH's continuing effort to diversify the overall workforce.

Last year NIH launched the UNITE initiative to identify and address structural racism within both the NIH-supported community and the greater scientific community. UNITE aims to establish an equitable and civil culture within the biomedical research enterprise and reduce barriers to racial equity in the biomedical research workforce. One important initiative was the Power of an Inclusive Workplace Recognition Project, which uses portraiture within NIH buildings and online to recognize the diverse members of NIH who have made significant contributions. This work was led by Sadhana Jackson, M.D., who wrote an opinion piece about this project. Dr. Jackson recognized that scientific institutions like NIH failed to acknowledge the contributions of diverse people at those institutions. Dr. Tabak encouraged the Board members to view the portrait installation next time they are on campus.

As part of its efforts to enhance DEIA, NIH piloted a program in the Intramural Research Program (IRP) that focused on hiring critical masses of early-career faculty who demonstrated commitment to inclusive excellence. After its success in the IRP, this effort was expanded into the extramural community through the Faculty Institutional Recruitment for Sustainable

Transformation (FIRST) program. FIRST has issued its first round of funding, and the response has been very positive.

Continued Commitment to Early-Stage Investigators (ESIs)

In 2014, after analyses from two Advisory Committee to the Director working groups (WGs) and the Office of Extramural Research, NIH made the commitment to increase its support of ESIs. The goal was to fund at least 1,100 ESIs per year; this number has grown steadily each year since 2015, and in 2022, NIH funded 1,589 ESI applicants. Institute and Center (IC) directors have pledged to continue this commitment to ESIs and plan to fund as many meritorious applications as possible. NIH is also monitoring who may be at risk of losing their initial NIH funding as new investigators and plans to balance its portfolios of funded organizations that have been overlooked or underfunded, including historically Black colleges and universities (HBCUs), Hispanic-serving institutions (HSIs), Tribal colleges and universities (TCUs), and institutions in rural areas.

Discussion

Dr. Coots thanked Dr. Tabak for his presentation, especially his updates about NIH's DEIA efforts. All institutions are dealing with the issue of improving DEIA.

Stephanie Reel, M.B.A., asked whether NIH tracks the diversity of its ESI-funded investigators. Dr. Tabak said that the percentage of ESI-funded investigators from minority populations is much higher compared with later-stage investigators; however, the overall number of ESI investigators who are Black or African American, Hispanic or Latino, and American Indian/Alaska Native is still very small. Ms. Reel said that institutions should commit to hiring diverse faculty and enrolling diverse students so that they will eventually become candidates for tenure or leadership positions. Dr. Tabak agreed and said that NIH and extramural institutions should work together to improve the diversity of graduate students, postdoctoral fellows, and faculty members so they can have long careers that are supported by NIH.

In response to a question from Dr. Devaskar, Dr. Tabak said that FIRST funding supports extramural researchers, but the program was piloted intramurally. NIH often tests programs through the IRP and takes lessons learned to create programs for extramural researchers.

Dr. Chin asked whether NIH could share its best practices for promoting DEIA and supporting diverse talent through the career pipeline with other institutions. Dr. Tabak said that although NIH does not have answers, the agency has learned a lot from its sessions with stakeholders. For example, through the stakeholder sessions, NIH leadership learned that people at a certain grade level were not afforded the opportunity for career advancement and leadership training. NIH leadership training criteria had an education level that was too high, leading to the exclusion of an overwhelming number of Black or African American, Hispanic or Latino, and American Indian/Alaska Native staff. As a result of this finding, NIH will reassess its grade-level criteria for leadership training.

In response to a comment from Mr. Baum, Dr. Tabak said that the success rates for ESI applicants is higher than standard success rates for NIH-funded researchers. The payline is extended for ESI applicants to fund more investigators. Board members can read more about ESI funding rates in July 2021 and July 2022 blog posts at the NIH Extramural Research website.

In response to a question from Ms. Royster, Dr. Tabak said that investigators from HBCUs, HSIs, TCUs, and rural institutions can reach out to program officers for more information on funding opportunities like FIRST.

NIH Clinical Center Chief Executive Officer Update

James Gilman, M.D., CEO, NIH Clinical Center (CC)

Dr. Gilman thanked the CCRHB and Dr. Coots for chairing the Board. He gave special thanks to Dr. Shannon for his service on the CCRHB and for being a source of sound advice to CC leadership.

CC Staffing Updates

Dr. Gilman said that there are still ongoing searches to fill three leadership positions at the CC: Chief Nurse Officer, Chief Financial Officer, and Chief of the Pharmacy Department. There are also two new vacancies: the position of Chief of the Department of Transfusion Medicine, which David Stroncek, M.D., is holding in the interim, and that of the Hospital Epidemiologist and Chief of the Hospital Epidemiology Service, which David Henderson, Ph.D., is filling at present.

Awards

Four honorees for the 2022 Clinical Recognition and CC Administrator of the Year Program will be announced at the next CC Town Hall on October 25. Two of the honorees are in the Staff Clinician of the Year category, one is in the Nurse Practitioner of the Year category, and one is in the Administrator of the Year category.

The 2022 NIH Director's Awards will be held virtually in early November. There are 157 CC awardees, 4 individuals, and 153 members of 16 groups. The 2022 CC CEO Awards will also be virtual and will be held on December 16. There are 134 nominations, totaling 835 nominees, being considered.

Average Daily Census (ADC)

The ADCs for 2021 and 2022 are still below the 3-year average of FY 2018–2020, but census trends are improving. Outpatient clinical visits have increased by 15%, and the number of new patients is up almost 10%. The average length of stay is decreasing slightly. Telehealth visits have stabilized to about 600 visits per month.

Patient Safety and the Clinical Center

The Centers for Disease Control and Prevention (CDC) changed their recommendations related to universal masking in health care settings. However, because of the number of immunocompromised patients present, the CC has not changed its masking policy at the hospital. Over the past 2.5 years, the CC has demonstrated that patients can be kept safe through masking. The CDC guidance is based on transient measures of COVID-19 transmission in the community, but it does not make sense for the CC to allow people to take their masks off in October, when viral activity is lower, and then put them back on in November and December, when COVID-19 and other viral activity is higher.

At the previous CCRHB meeting, there was a question about how the CC ensures that patient safety and clinical research efforts are coordinated. This coordination effort is led by Dr. Schor, the Acting DDIR, who is the institutional official and interface between the CC and the U.S. Food and Drug Administration (FDA). The Deputy Director works with the Office of Patient Safety and Clinical Quality (OPSCQ), led by David Lang, M.D., M.P.H., and the CC CEO. Updates from the clinical side are communicated through the Safety Tracking and Reporting System (STARS) and the Patient Safety Huddle notes and shared daily to the Office of Human Subjects Research Protections (OHSRP), which is led by Jonathan Green, M.D., M.B.A. The Office of Research Support and Compliance (ORSC), which is led by Virginia A. Guptill, Ph.D., reports to the CC executive leadership every 2 weeks; the DDIR meets with OHSRP, ORSC, and the CC CEO twice a month; and the ORSC leadership, CC CEO, and DDIR meet once a month for the Sterile Products for Human Administration Committee meeting. All of these meetings and the frequency of communications ensure a positive patient experience and safety during the research process.

Future of Work

The CC is currently working to define the future of work and get employees back to the CC. This was a major discussion point during a recent NIH Leadership Forum meeting, since ICs are also dealing with this issue. Now is the right time for the CC to move back toward in-person work; however, this will not be an easy transition.

The CC's work can be divided into transactional and relational work. Transactional work is the work that is part of the job description, but how employees communicate and interact through relational work contributes to transactional work. This communication can be lost through virtual options and full-time virtual work may be perceived as misuse of government resources in some cases. The CC will find a solution to slowly begin bringing people back to work in person.

Clinical and Safety Performance Metrics

Dr. Gilman reminded the Board that the quarterly report of patient and staff safety metrics, previously presented at Board meetings by Dr. Lang, the Chief of the OPSCQ, will now be made available on the CC website 1 week after the CCRHB meeting. Board members with questions or requests for the presentation of additional information at meetings can contact Dr. Lang or Dr. Gilman.

Discussion

Many CCRHB members commented that their institutions are keeping mask requirements within their hospitals and clinical centers.

Julie A. Freischlag, M.D., asked about any challenges with staffing nurses at the CC. Dr. Gilman said that there are challenges with recruiting and retaining nurses, particularly specialty nurses.

Dr. Coots said that his institution was able to lower its administrative costs by shifting some workers to virtual; however, the leadership realized that the workplace culture was suffering. The institution is working to create swing spaces and bring staff on site once or twice a week as a way to build relationships and support the organization's culture.

Mr. Baum said that there are software tools that support hybrid patient rounding and clinical visits, so there can still be a mix of virtual and in-person work. Dr. Gilman said that the CC plans to use some of those tools, but they do not address the issue of workplace culture. These tools do not support the teamwork and collaboration between specialized patient care teams that occur in person. Mr. Baum agreed that these tools do not replace personal presence, but they do give patients a way see their friends and family if there are visitor restrictions. Dr. Gilman said that the CC has facilitated virtual visits with patients' families throughout the pandemic.

Clinical Research at the Clinical Center: Past and Present

John I. Gallin, M.D., Chief Scientific Officer and Scientific Director, CC, and NIH Associate Director for Clinical Research

Dr. Gallin expressed his excitement at sharing his passion for the CC with the CCRHB. Many people made this research possible—particularly patients, many of whom gave their lives for this research. The CC is hallowed ground, and many people have said that there is no other hospital like the CC.

The story of the CC starts on July 1, 1944, when Congress passed the Public Health Service Act, which authorized the establishment of the CC. On July 8, 1947, Congress appropriated $60 million to build the CC. The CC's vision was established by President Harry Truman, who emphasized the importance of research that could help detect and stop diseases in their early stages.

One of the major features that sets the CC apart from other hospitals is that it provides free care for patients from all over the country and the world. Another is that every patient participates in one of the 1,500 clinical research protocols at the CC. The CC is also surrounded by research laboratories on campus, and the interaction between the CC and NIH laboratories has led to 33 Lasker Awards and seven Nobel laureates over the years.

In 1953, the CC's first medical board was formed. The board issued the "Guiding Principles in Medical Research Involving Humans," which required prospective review of all human research at the CC, including a detailed review of the informed consent process. This policy served as the basis for all national IRBs.

The CC also has many special resources that enable its studies, including a biomechanics laboratory; metabolic chambers to study the physiology of people with obesity and wasting syndromes; the Center for Cellular Engineering, which manufactures chimeric antigen receptor T-cells (CAR-T cells) and other cellular-based therapeutics; a magnetic resonance imaging (MRI) center with 30 MRI machines in or near the CC; a positron emission tomography (PET) research center with three cyclotrons for manufacturing imaging probes; a high-containment clinical studies unit; a strong healthy volunteer program; and a bioethics department.

Selected Accomplishments at the Clinical Center

Dr. Gallin reviewed some accomplishments at the CC in several different areas: cancer, transfusion medicine, hematology and sickle cell anemia, heart disease, infectious diseases, mental illness, endocrinology, and techniques and devices. These accomplishments are focused

in three areas: pathophysiology of disease, first-in-human trials with new drugs and devices, and rare diseases.

Cancer

- 1958: Min Chiu Li, M.D., and Roy Hertz, M.D., discovered that methotrexate can be used to treat choriocarcinoma, the first successful treatment of human solid tumors and the beginning of chemotherapy for cancer.
- 1964: Emil Frei III, M.D., and Emil J. Freireich, M.D., found the cure for childhood acute lymphocytic leukemia, using chemotherapeutic approaches.
- 1965: James Holland, M.D., John Zeigler, M.D., Vincent DeVita, M.D., and Charles Gordon Zubrod, M.D., helped to make chemotherapy a standard treatment for cancer.
- 1988: Steven Rosenberg, M.D., Ph.D., treated metastatic melanoma with cell transfer therapy and later showed this treatment provided a durable and complete response.
- 1993: W. Marston Linehan, M.D., discovered the genetic basis and management of hereditary kidney cancer.
- 2001: Ira Pastan, M.D., and Robert Kreitman, M.D., used immunotoxin BL22 to treat hairy cell leukemia.
- 2008: Peter Pinto, M.D., Bradford Wood, M.D., and Peter Choyke, M.D., FACR, conducted an MRI-ultrasound fusion-guided prostate biopsy.
- 2017: James Kochenderfer, M.D., and colleagues used CAR-T cells to treat lymphoma.

Transfusion Medicine

- 1956: Wallace Coulter and George Brecher, M.D., developed the Coulter model S automatic blood counter.
- 1961: Allan Kliman, M.D., conducted the first plasmapheresis and showed that plasma is a rich source of platelets.
- 1965: George Judson from IBM and Dr. Freireich created the continuous flow blood separator.
- 1964: Harvey Alter, M.D., co-discovered the Australia antigen, which is the coding antigen for hepatitis B.
- 1970: Dr. Alter's work helped blood banks switch to all volunteer donors, reducing post-transfusion hepatitis from about 30% to 11%.
- 1989: Dr. Alter co-discovered the hepatitis C virus, a discovery that won him the Nobel Prize in 2020.

Hematology and Sickle Cell Anemia

- 1995: Neal Young, M.D., developed a treatment for aplastic anemia with antithymocyte globulin and cyclosporine.
- 1995: Griffin Rodgers, M.D., MACP, found that hydroxyurea is an effective treatment for sickle cell anemia.

- 2019–2022: Courtney Fitzhugh, M.D., and John Tisdale, M.D., are testing bone marrow transplantation and gene therapy for treating sickle cell anemia.

Heart Disease

- 1957: Eugene Braunwald, M.D., and Andrew Glenn Morrow, M.D., described idiopathic hypertrophic subaortic stenosis for the first time, and Dr. Morrow developed surgical procedures to treat people with this issue.
- 1960: Nina Starr Braunwald, M.D., conducted the first successful mitral valve replacement.
- 1961: Donald Fredrickson, M.D., and Robert Levy, M.D., discovered the genetic basis of Tangier disease, leading to the understanding that high lipid levels are a risk for coronary heart disease.
- 2002: Phillip Gorden, M.D., described the use of leptin to treat lipodystrophy.

Infectious Disease (Vaccines)

- 1987: Rachel Schneerson, M.D., and John Robbins, M.D., developed the *Haemophilus influenzae* meningitis vaccine.
- 1972–1994: Stephen Feinstone, M.D., and Robert Purcell, M.D., discovered and made a vaccine for hepatitis A, Dr. Purcell and his team made a vaccine for hepatitis B, and Albert Kapikian, M.D., and his team, including Richard Wyatt, M.D. and Harry Greenberg, M.D., made the first rotavirus vaccine.
- 1997: Gary Nabel, M.D., Ph.D., and Barney Graham, M.D., Ph.D., developed the Ebola vaccine and administered it to the first human recipient.
- 2005: Douglas Lowy, M.D., and John Schiller, Ph.D., developed the technology for the human papillomavirus vaccine.
- 2020: Kizzmekia Corbett, Ph.D., and Dr. Graham developed the technology for the COVID-19 vaccine and administered it to the first patient.

Infectious Disease (Acquired immunodeficiency syndrome [AIDS])

- 1982–1985: Dr. Fauci, Dr. Lane, and colleagues identified HIV as the pathogen that causes AIDS, and Robert Gallo, M.D., developed a screening test for HIV (which he called human T-lymphotropic virus type III [HTLV-III]).
- 1987–1990: Samuel Broder, M.D., developed the first treatments for HIV, including azidothymidine (AZT) in 1987, 2′-3′-dideoxycytidine (ddC) in 1988, and 2′-3′-dideoxyinosine (ddI) in 1990.
- 1984–2002: Joseph Kovacs, M.D., genetically sequenced and developed new diagnostic tests for *Pneumocystis carinii* pneumonia, and Henry Masur, M.D., developed the national guidelines for management of HIV.

Infectious Disease (Immunology)

- 1982: Stephen Straus, M.D., conducted the first clinical trials using acyclovir to treat genital and oral herpes.

- 1994: Robert Nussenblatt, M.D., and colleagues developed a sustained-release ganciclovir implant for cytomegalovirus retinitis.
- 1997: Julie Segre, Ph.D., Tara Palmore, M.D., and David Henderson, M.D., used microbial genomics to understand hospital infection outbreaks.
- 2021: Sameer Kadri, M.D., M.S., studied the survival of COVID-19 patients in 558 U.S. hospitals and ensured that the interhospital transfer of COVID-19 patients was safe. Warren Leonard, M.D., and John O'Shea, M.D., found that JAK inhibitors can be used to treat autoimmune and allergic diseases, as well as COVID-19.
- 2022: Daniel Chertow, M.D., M.P.H., published a study in *Nature* that used autopsies to find that SARS-CoV-2 can persist in the human brain as long as 230 days after symptom onset.

Mental Illness

- 1969: Frederick Goodwin, M.D., conducted the first clinical trials of lithium to treat depression and mania.
- 1977: Louis Sokoloff, M.D., discovered 2-deoxy-D-glucose and developed PET scanning.
- 1985: Judy Rapoport, M.D., was the first to describe obsessive-compulsive disorder and treat the disorder with clomipramine.
- 1994: Dr. Rapoport was the first to treat childhood schizophrenia with clozapine.
- 1998: Susan Swedo, M.D., identified pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS).
- 2010: Carlos Zarate, Jr., M.D., used ketamine to treat depression and suicidal ideation.
- 2012: Peter Schmidt, M.D., and David Rubinow, M.D., were the first to describe premenstrual dysphoric disorder and used fluoxetine as a treatment.
- 2016: Dr. Zarate used esketamine to treat depression without addiction.
- 2020: Ellen Leibenluft, M.D., described disruptive mood dysregulation disorder in children to differentiate irritability from pediatric bipolar disorder.
- 2012–2021: Maryland Pao, M.D., developed a suicide screening tool.

Endocrinology

- 1972: Jesse Roth, M.D., FACP, discovered insulin receptors.
- 1985: Lynnette Nieman, M.D., and Lynn Loriaux, M.D., Ph.D., discovered the glucocorticoid antagonist RU 486 as a treatment for Cushing's syndrome.
- 2017: Forbes D. Porter, M.D., Ph.D., identified intrathecal 2-hydroxypropyl-beta cyclodextrin as a treatment for Niemann-Pick disease. Jack Yanovski, M.D., Ph.D., defined the importance of the melanocortin-3 receptor and brain-derived neurotrophic factor in obesity.
- 2013–2022: Debbie Merke, M.D., M.S., defined congenital adrenal hyperplasia management.

Techniques and Devices

- 1963: Ayub Khan Ommaya, M.D., Sc.D., developed the Ommaya reservoir for access to the central nervous system (CNS).
- 1969: John Doppman, M.D., created a method to locate parathyroid glands.
- 2022: Andrew Mannes, M.D., M.E., M.B.A., and colleagues created a low-cost 3D-printed miniature ventilator.
- 2016–2022: Diane Damiano, Ph.D., and Thomas Bulea, Ph.D., developed external robotic devices to improve motor tasks in children with cerebral palsy.

Future Challenges

While the CC has accomplished a lot, it still faces many challenges, including the recruitment and retention of the best clinical researchers. Also, increased efforts to promote DEIA will be needed. As demonstrated by the timeline of accomplishments provided above, there is not much diversity among the featured investigators. Among those 80 investigators, only 11 (14%) were women, five were underrepresented minorities (6%), and three (4%) were African Americans. The CC also faces challenges with its budget and physical plant.

Some future-looking questions for the CC include whether the center should be able to study more infected patients during the next pandemic and whether there should be more investment in health-related social issues, such as health behavior and health disparities research.

Discussion

Overall, the Board members were very impressed by and appreciative of the presentation. Ms. Reel said that the world probably is not fully aware of the CC's contributions to medicine. She shared a personal story about a friend with metastatic cancer and asked about what NIH can do for such patients. Dr. Gallin said that patients can visit ClinicalTrials.gov to search for trials, with filters by region and disease of interest. Patients can also visit the CC website to search for trials. The Office of Patient Recruitment has a hotline for people who do not have internet access or who have additional questions.

Ms. Royster said that there should be a PBS documentary or some sort of public-facing presentation of the CC's accomplishments to promote public awareness. As a patient who has been helped by the CC, she said that other people need know about this amazing work. Dr. Gallin said that there was a two-part television series, "First in Human" about the CC, but more public awareness would be great. Many people do not even know that there is a hospital at NIH. Dr. Coots added that every superhero needs a theme song, so NIH should publicize its CC superheroes.

Impact of Research at the Clinical Center

George Santangelo, Ph.D., Director, Office of Portfolio Analysis (OPA), NIH

Dr. Santangelo and his team used artificial intelligence/machine learning (AI/ML) methods to analyze the outputs of the NIH Clinical Center research at scale between 2017 and 2020. This information, which can be found on OPA's website, can help decision makers better understand their research portfolios.

CC researchers authored 931 publications between 2017 and 2020.

- 33.6% had evidence of clinical impact, meaning the publication appeared in a clinical journal, was cited by one or more clinical journal, or was cited by a clinical trial that has reported results.
- 4.1% had technical impact, meaning the publication was cited by a patent.
- 2.0% had both clinical and technological impact, which is important because it is most indicative among papers that lead to drug or device approval by the FDA.

OPA has developed computational approaches that define what constitutes a distinct topic in an unbiased fashion, determine the age and rate of progress for each research topic, identify emerging areas of research, and predict which topics will produce transformative breakthroughs in the coming 2 to 12 years. This computational way of predicting which topics will produce breakthroughs has a pending patent application describing this methodology.

The first area of OPA's analysis was finding which topics were represented in publications authored by CC researchers and how productive these topic areas were. The AI/ML analysis of the 931 publications from the CC between 2017 and 2020 divided the publications into 13 topic areas. The computer extracted AI labels, or nearest word or terms, using semantic analysis, which is the quantitative representation of the central tendency for each topic. Dr. Santangelo shared a map of the topics that showed the number of publications for each topic category, represented by the number and the size of a circle, and AI labels for each topic were listed under each. The map also had lines connecting certain topics, with the thickness of the line reflecting the topic similarity. In general, these analyses can separate out more fundamentally focused research from patient-focused research. This analysis was used to determine the number of publications that were cited by clinical studies, which include clinical trials or guidelines, to understand how clinically impactful the research is.

Next, OPA reviewed how extensive collaborations between the CC and other NIH ICs in the IRP, within the IRP, and between the CC and external researchers were, as well as whether these collaborations correlated with increased productivity. The analysis showed the percentage of publications from CC laboratories, IRP laboratories, and extramural laboratories that were limited to a single intramural laboratory, meaning the publication had no identified collaborations, and that were intra-IC publications, between two ICs, between three ICs, or between three or more ICs. Even though there were fewer intra-IC publications with CC labs, the publications resulting from collaborations between the CC and two or three ICs is much greater. Similarly, the representation of collaboration with extramural laboratories is quite healthy.

When the percentage of CC publications that involved collaborations with individual ICs was reviewed, the ICs with the most collaborations with the CC included NCI, NIAID, and the National Heart, Lung, and Blood Institute (NHLBI).

OPA's next analysis involved finding how influential publications were. The analysis showed a strong correlation between the extent of collaboration and productivity, as demonstrated by the number of citations by clinical trials, patents, and clinical trials and patents. Both the CC and the IRP at large show that correlation.

The final part of OPA's analysis was mapping the rate of progress in CC areas of research. Some questions that this analysis can answer are which topics have the highest share of CC publications, what percentage of publications in the CC topics were funded by NIH overall, and what percentage of publications in the CC reported results of clinical studies.

OPA plotted topics based on the age of the topic in years (0 to 50 years old) and the relative rate of progress. The topics in this analysis were defined by the co-citation network of the publication, compared to the topics in the first part of the presentation that were determined by the semantic content of the publications. The size of the circle represented the total number of published studies, and the heat mapping showed the number of studies published by CC labs. This analysis identified fast- and slow-moving topics to help leadership understand where the science is making the most impact.

The goal of this work by OPA was to provide both a simple way for casual users to engage with these data and a detailed and analytic approach to reviewing the biomedical research landscape at large (e.g., publications, clinical trials, grants) for more detailed-oriented power users. OPA is developing an analytical tool will be released to the public, and people can contact Dr. Santangelo if they are interested in signing up as beta testers.

Overall, CC researchers published 931 studies between 2017 and 2020.

- 43% of CC publications were collaborative with other ICs.
- 60% of CC publications were collaborative with researchers outside NIH.
- CC principal investigators (PIs) collaborated the most with researchers from NCI and NIAID.
- 95% of CC PIs had collaborators in another IC, outside of NIH, or both.
- Collaborative publications were more influential and generally had greater clinical and technological impact.

CC publications focused on 13 distinct topics. The topic that had the highest number of clinical citations was defined by the terms: intensive care units (ICUs), hospital mortality, hospitalization, critical illness, and the first 48 hours. The topic with the highest numbers for patent citations included publications defined by the terms ground truth, 3D segmentation, algorithms, accuracy, and deep learning. The prominent topic for publications from intra-NIH collaborations was focused on CAR-T cell therapy, hematologic neoplasms, alemtuzumab, homologous transplantation, and rituximab. Ethical issues was the most common topic for publications from external collaborations.

Discussion

Dr. Chin asked whether this tool could be used by extramural institutions, so that they analyze their own portfolios. Dr. Santangelo said that although the methods presented have not been published, the methodology and code will be shared soon. The goal is to be able to have investigators download data through an application programming interface (API) and conduct these analyses. The data will mirror those in the NIH RePORTER but support further analyses. Dr. Chin added that many academic medical centers fail to understand their portfolios, so this will be an amazing tool.

In response to a question from Mr. Baum, Dr. Santangelo said that *iSearch* is the tool that is accessible to NIH staff to conduct analyses similar to those that have been done by OPA. *iSearch* Analytics will be released soon and will be available for use by extramural researchers and institutions. Dr. Tabak said that he uses the NIH-internal version of this tool all the time to understand the influence of certain publications or learn more about publication impact as it relates to promotions and tenure decisions. This tool is extremely useful and should be shared with extramural colleagues.

Gene Therapy of Infants with GMI Gangliosidosis

Cynthia Tifft, M.D., Ph.D., Deputy Clinical Director and Senior Clinician, Medical Genetics Branch, National Human Genome Research Institute (NHGRI)

Patricia Todd, DNP, RN, APRN, PCNS-BC, CPEN, Pediatric Clinical Nurse Specialist, Critical Care and Sedation Services, CC Nursing Department, NIH

Dr. Gilman reminded the Board members that the July meeting included a status report about the 2019 Clinical Center Strategic Plan that mentioned the major efforts in caring for two infants with GM1 gangliosidosis. This presentation provides additional details on those efforts and sets up a presentation about a proposal to use a similar approach to treat other pediatric diseases.

Dr. Tifft said that GM1 gangliosidosis is part of a large family of disorders known as lysosomal storage disorders (LSDs), multisystem diseases characterized by lysosomal dysfunction. There are more than 70 LSDs, each with their own inherited genetic mutation, and most LSDs are autosomal recessive. Most LSDs have a progressive neurodegenerative clinical course plus systemic manifestation. LSDs have symptom onset in infancy, childhood, and sometimes adulthood. LSDs are individually rare but collectively affect 1 in 5,000 live births.

GM1 gangliosidosis is an autosomal-recessive LSD caused by biallelic mutations in *GLB1* that produce a deficiency in the hydrolytic enzyme lysosomal beta-galactosidase. The GM1 protein is at the top of the sphingolipid degradation pathway; beta-galactosidase converts GM1 ganglioside to GM2 ganglioside. Like its more well-known cousin, Tay-Sachs disease, GM1 gangliosidosis is a rare and uniformly fatal neurodegenerative disorder that has no approved therapies. The disorder is panethnic, with an incidence of about 1 per 200,000 live births, but it is more common in people from Malta and Brazil and among the Roma, where there are founder mutations. Newborn screening is not yet available for GM1 gangliosidosis.

GM1 gangliosidosis is a multisystem disorder that predominantly affects the central nervous system. The accumulation of toxic storage materials in the CNS and peripheral tissues leads to progressive cerebral atrophy and neurodegeneration. Infants with GM1 gangliosidosis have a cherry-red macula or "cherry-red spot." Patients also have varying degrees of hepatosplenomegaly, skeletal dysplasia, and cardiomyopathy.

GM1 gangliosidosis is a disease continuum, meaning that the disease severity increases as the residual enzyme activity decreases.

- **Infantile (type I) GM1 gangliosidosis**. The onset of symptoms starts before 6 months of age. The two patients in the aforementioned clinical trial have infantile GM1 gangliosidosis. These patients have severe hypotonia, developmental plateauing around

the time of sitting, hepatosplenomegaly, and cherry-red maculae. They develop progressively debilitating seizures, which increases aspiration risk. Patients usually succumb to their disease by aspiration, pneumonia, or seizures before the age of 2.

- **Late-infantile (type IIa) GM1 gangliosidosis.** These patients meet their milestones by 12 months, then symptom onset occurs between 12 and 24 months. They have impaired ambulation, decreased cognition, and only some speech (with few words) that is eventually lost. They develop seizures and usually die in their mid-teens.
- **Juvenile (type IIb) GM1 gangliosidosis.** Patients typically do fine in their early years but finish kindergarten developmentally worse than when they started. They have impaired ambulation, with increased falls, and progressive stuttering or dysarthria, and they eventually lose the ability to speak. They also exhibit skeletal disease and decreased cognition. These patients can survive into their fourth decade; two of Dr. Tifft's patients with type IIb GM1 gangliosidosis are in their early 30s.
- **Adult (type III) GM1 gangliosidosis.** Symptom onset for type III occurs during adulthood. Type III gangliosidosis is not very common in the United States but is more common in Japan. These patients develop normally until early adulthood and then develop dystonia, dysarthria, and variable times of death. They often die from other causes before they die of their GM1 gangliosidosis.

Later onset of disease means greater variability in disease progression; infantile disease has a fairly narrow window of onset and a fairly standard decline, but the onset of symptoms in juvenile disease is quite variable and the range at which patients succumb to their illness is even more variable.

Dr. Tifft's team has been conducting a natural history study for GM1 gangliosidosis at NIH for the past 10 years. There are 41 patients, including 30 probands, and the rest are affected siblings. Among the 41 patients, 17 are late-infantile and 24 are juvenile patients. The study has demonstrated that the time between symptom onset and diagnosis is very long: 17.5 months for late-infantile patients and 10 years for juvenile patients. This study has also identified adaptive behavior plateaus followed by declines over time. Progressive brain atrophy tracks with declines in behavior and cognition, and elevation of unique pentasaccharide biomarker can provide a readout of treatment efficacy.

Dr. Tifft's team has also begun a gene therapy trial. Stage 1 of the trial is a dose-ranging study where six late-infantile/juvenile GM1 gangliosidosis patients were treated with a low dose of intravenous (IV) adeno-associated virus serotype 9 (AAV9) gene therapy vectors and three late-infantile/juvenile patients were treated with a high dose. The study also administered low-dose AAV9 treatment of two infantile patients and plans to treat up to three infantile patients with a high-dose AAV9 treatment. All patients received immune modulation with rituximab, sirolimus, and glucocorticoids, and all treated patients are doing well after receiving the gene therapy.

The eligibility criteria for late-infantile/juvenile patients include genetic and biochemical diagnosis of GM1 gangliosidosis, AAV9-negative antibody status, and a score on the Vineland Adaptive Behavior Scale of at least 40, meaning that there is some behavioral function left so that improvement or decline can be detected. Infantile GM1 gangliosidosis patients need to be between 6 and 12 months of age and have documentation of the disease.

The primary endpoint of this study is safety and tolerability. The secondary and exploratory endpoints include the following:

- Disease severity as measured by the Clinical Global Impressions Scale and upright and floor mobility scales
- Developmental changes assessed by the Vineland-3 Adaptive Behavior Scale and the Bayley Scale of Infant Development
- Changes in brain volume detected by MRI and N-acetylaspartate by magnetic resonance spectroscopy after 1 year
- Biomarkers of disease, including beta-galactosidase enzyme activity in serum, GM1 gangliosides in cerebrospinal fluid (CSF), and pentasaccharide biomarker in serum, urine, and CSF.

The first juvenile patient received gene therapy on May 8, 2019, and the group celebrated with a tea party.

Dr. Todd said that support from executive leadership helped to ensure clinical readiness and the care of infants at the CC. Key stakeholders from 14 CC departments and four services, representatives from Children's National Health System, and the gene therapy research team assessed this study and identified the medications, treatments, and procedures that these patients would need. The deep dive began with a failure mode and effects analysis (FMEA), a process that is often used in the CC for high-risk studies. For this first-in-human infant gene therapy protocol, the FMEA identified 194 potential risks in eight major areas: pre-enrollment/pre-arrival, baseline testing, procedures, immune modulation treatment, discharge to a local area, equipment, emergency response, and education, training, and competencies. The analysis helped identify vulnerabilities and ensured safety measures were in place across the CC before any of these children enrolled.

The FMEA revealed specific resources that were required to mitigate some of the risks. The emergency response plan needed to be expanded to include additional after-hours intensivist coverage and changes to the structure of the Code Blue team. The review revealed that some departments did not have supplies needed for the care of infants, including low volume research lab tubes, breastfeeding supplies, and emergency equipment. Policies and procedures required that best practices models be developed and used. It also became apparent that additional training for clinicians was needed. At NIH, children under 3 years old were not historically admitted to the pediatric unit of the CC; since the patients in the trial were going to be admitted and have procedures and tests throughout the CC, expanding clinical competency was paramount.

In taking a closer look, the FMEA identified several gaps in the Nursing Department related to equipment, emergency response, education, training, and competencies.

- **Equipment.** Two identical infant supply carts were created for the pediatric unit and for the code team in the ICU. The CC also provided breast pumps and developed policies for breastfeeding mothers. IV start equipment was needed for infant-sized access, and strategies for reducing the volume of blood collected were reviewed to reduce the amount of blood taken for labs. Using the Institute for Healthcare Improvement toolkit, the team developed a cause-and-effect diagram to depict the complexities of the process of

drawing blood at the CC, finding that research bloodwork and clinical bloodwork were often ordered separately, and patients who were on multiple protocols caused overuse of lab tests. Also, blood samples were drawn in large, adult-sized collection tubes, an identified risk for infant patients. Once the research team reviewed these results and the protocol, the research lab collection volume was reduced by 70%.

- **Emergency response.** Infant equipment was added to the code cart. The weight-based code and infusion sheets were originally developed with 5-kilogram increments and were not made for pediatric patients. The team further broke down the weight-based code and infusion sheets into 1-kilogram increments between 5 and 15 kilograms. The Children's National intensivist and respiratory therapist were incorporated into the code and team response structure. In the event of a code, the Children's National intensivist would run the code.
- **Education and training.** The team realized that nurses and staff would need to be educated and trained, since patients would be visiting many areas of the CC, including the pediatric inpatient unit, the ICU, the post-anesthesia care unit, and interventional radiology. All nurses were trained in the care of infants using didactic and hands-on skills labs to learn intraosseous placement, rapid sequence intubation, fluid resuscitation, hemodynamic drips, and arrhythmia management. Nurses and staff were then trained in a simulation lab where multidisciplinary NIH teams ran through four scenarios that these patients could experience: anaphylaxis, supraventricular tachycardia, seizures, and shock. These multidisciplinary NIH teams and the Children's National intensivist and respiratory therapist conducted in situ simulations in the pediatric wing. Overall, education and training was divided into three phases: Phase 1 included eight lectures and eight skill stations, phase 2 included 24 integrated in-lab simulations with CC providers, and phase 3 included five in situ multidisciplinary simulations with Children's National Hospital providers.
- **Competencies.** The team reviewed competencies, policies, and procedures that potentially would need to be initiated, reviewed, or updated to address the care of infants. The procedures fell into three categories: venous access placement and management, chemotherapy/biotherapy administration of rituximab in infants, and breastfeeding/expressed breast milk.
    - ***Venous access place and management***. The CC has not cared for small children, who would need central access. The team decided on a peripherally inserted central catheter (PICC); patients would be sent to Children's National for that placement if needed. The Nursing Department revised their policies to include flushing guidelines and the care of an infant with a PICC line.
    - ***Chemotherapy/biotherapy*.** The CC does not commonly administer chemotherapy/biotherapy to infants. The team identified evidence-based practice standards and contacted the Association of Pediatric Hematology/Oncology Nurses to develop and expand the CC's policies related to the care of infant patients receiving rituximab.

- ***Breastfeeding/expressed breast milk.*** The CC did not have well-established breastfeeding policies. Developing these policies was a large effort that involved input from many departments, including nutrition, nursing, infection control, and the lactation room coordinator. This effort also involved developing an infrastructure of refrigerators and milk-heating equipment.

The team realized that the methods of education, training, and competency that were developed for this protocol could be transferable to new protocols; in fact, these methods were integrated into one or two additional protocols. This endeavor demonstrated the importance of close monitoring of training plans and safety and best practices in blood collection. At present, the lab and material management are evaluating low-volume collection tubes that can be used for both pediatric and adult patients throughout the CC.

In August 2021, the Pediatric Planning Group (PPG) was established to evaluate pediatric care at the CC and assess the feasibility of expanding patient volume, increasing the ability to manage higher-acuity patients, and reducing the lower age limit of admission from 3 years to 6 months. Subgroups were created that provided detailed recommendations in three areas: pediatric emergency management, pediatric critical care, and pediatric subspecialty coverage. A proposal with detailed recommendations has been submitted to the CC leadership.

Discussion

Ms. Reel thanked Dr. Tifft and Dr. Todd for their work and said that it is hard to see children sick, especially when they are suffering from a tough disease. This work is important and inspirational; it gives families hope and optimism.

Dr. Devaskar asked how long the study team would follow the gene therapy trial participants, especially the infants. Dr. Tifft said that two infantile patients have been treated; the first patient unfortunately succumbed to the illness in March 2022, and the second patient was seen a few months ago. FDA requirements for Phase 1 AAV9–based gene therapy trials require that the team follow patients for 5 years, but this may not happen, because patients with infantile GM1 gangliosidosis are quite fragile.

In response to Mr. Baum's question, Dr. Gilman said that the protocol did not make any changes to visitation policy, but did provide special accommodations for patients' families, especially the families of infant patients.

Dr. Shannon said that as long as he has been a part of the CCRHB, there have been discussions about the hope and opportunity associated with gene therapy for children. The efforts that went into creating a safe environment to begin this work are incredibly impressive and represent the can-do attitude that the CC has demonstrated for many years. The possibilities are endless as this work continues, so kudos to the team creating the resources needed to treat these children.

Research in Pediatric Patients in the Clinical Center

James Gilman, M.D., CEO, NIH CC

Dr. Coots said that the CCRHB received materials ahead of the meeting to review: a formal report from the PPG and a draft charter for a WG that would be put to a vote. The CC will send hard copies of any of these materials to Board members if needed.

Dr. Gilman said that as the CC was able to undertake the efforts to prepare to care for infantile GM1 gangliosidosis patients using additional resources from a commercial partner for the gene therapy study. Without this type of support, it became clear that the CC could not conduct this type of assessment for every pediatric protocol. However, the CC could create a platform to prepare for human trials in younger and smaller patients.

The CCRHB has discussed pediatric research for many years. At the fifth meeting of the CCRHB, in 2017, Dr. Gilman described how the CC had cared for pediatric patients and wanted to expand the CC's capabilities. There was also a recommendation from the 2017 Engagement Report project that the CC should seek funding to enhance services provided to pediatric patients at the inpatient, outpatient, and consultative levels. At a CCRHB meeting in 2018, there was a presentation by CC pediatric leaders Deborah Merke, M.D., M.S., Krista Cato, M.H.A., RN, and Zenaide Quezado, M.D., who further expanded on the currently available CC pediatric services and areas of focus for the CC pediatric population.

The CC's previous efforts to care for pediatric patients had some limitations; the CC could only care for pediatric patients who were more than 3 years old and weighed more than 15 kilograms. At the CC, pediatric research begins with the establishment of a protocol and an assessment of the disease process of those children to anticipate their care needs. There is also a risk assessment related to the disease to understand any treatments needed and any complications that might occur. Then education, training, task organization, and, sometimes, contract partners are used to mitigate any potential risks and provide capabilities that are not already available to the CC. Once all this is done, the outcomes of these efforts are reviewed, and a go/no-go decision about the protocol is made. The CC Nursing Department and the Pediatric Care Committee play a huge role in this process. Dr. Todd's presentation explained various parts of this process, such as the FMEA and didactic simulation. After the experience with reviewing the GM1 gangliosidosis protocol, the CC established the PPG to find a way to easily reproduce this process for other pediatric protocols.

The PPG is chaired by William Gahl, M.D., Ph.D., who is the Director of the Undiagnosed Diseases Program at the CC and is a Senior Investigator in the National Human Genome Research Institute (NHGRI). The PPG's charter was approved by the Medical Executive Committee and the CC Governing Board, which is made up of IC Directors. The PPG divided itself into three subgroups: pediatric emergency management, pediatric critical care, and pediatric subspecialty coverage. In February 2022, the PPG report was presented to the CC Governing Board, who requested an external review by pediatric thought leaders. This led to the development of the CCRHB Pediatrics WG.

The PPG's report recommended that the CC should partner with a variety of pediatric specialists and subspecialists and establish a robust contractual arrangement with provisions for additional services at the CC, in the form of a small in-house pediatric ICU. This infrastructure would allow

the CC to repeat the experience with the GM1 gangliosidosis protocol for a number of other pediatric diseases. The estimated total cost for these proposals would be approximately $7.8 million per year, with initial costs around $5 million.

The major question that needs to be answered is whether the CC can provide more opportunities for early Phase I clinical trials in diseases of infancy and childhood. As mentioned by Dr. Gallin, the CC does not bill patients, and under that business model, there needs to be consideration of whether this additional work is advisable, feasible, and safe. There is also the issue of resources, such as adding a small number of organic capabilities and partnering with hospitals or health systems that have a full complement of pediatric capabilities, including specialties and subspecialities and services.

These questions are being taken on by the CCRHB Pediatrics WG, which is chaired by Candidate CCRHB member, Dr. Devaskar, and composed of a group of external pediatric experts. Dr. Devaskar was recommended to chair the WG by Diana Bianchi, M.D., the Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and Dr. Schor, the Acting DDIR. Each WG member is the chair of pediatrics at their institution and is responsible for providing care for children. They come from a variety of different institutions; some are from stand-alone pediatric hospitals, and some work in pediatric hospitals that are embedded in larger medical centers. None of the members of the WG are from the D.C. metro area, which would introduce a conflict of interest.

The members of the WG are:

- Clifford W. Bogue, M.D., Yale New Haven Children's Hospital
- Tina L. Cheng, M.D., M.P.H., Cincinnati Children's Hospital Medical Center
- Terence S. Dermody, M.D., UPMC Children's Hospital of Pittsburgh
- Donna Martin, M.D., Ph.D., University of Michigan
- D. Wade Clapp, M.D., Riley Hospital for Children
- Jordan S. Orange M.D., Ph.D., NewYork-Presbyterian Morgan Stanley Children's Hospital
- Gary A. Silverman, M.D., Ph.D., St. Louis Children's Hospital

The WG will meet virtually, and CC staff will provide additional data, information, capabilities, and documents that will be relevant to their review and recommendations. The WG will review the PPG's report and other relevant materials and provide recommendations on whether the CC is capable of conducting this type of pediatric research and what steps it needs to take to be successful. The goal is for the WG to deliver this report to the CCRHB for their review by the February CCRHB meeting. Once it receives consensus approval from the CCRHB, the report will be shared with the CC CEO and NIH Director.

The CCRHB received a draft of the WG's charter ahead of the meeting, and it was reviewed and approved by the CC Governing Board. Dr. Gilman requested a vote from the CCRHB to approve the charter.

Discussion

In response to a question from Dr. Coots, Dr. Gilman said that the goal is for the WG to provide a report to the CCRHB in February, but it may be delayed if the WG needs more time.

Dr. Coots requested a vote on the WG's charter and the plan to have the WG's report presented in February or, if necessary, June. The vote was unanimous, and the motion carried.

Dr. Devaskar thanked the Board for their unanimous vote and said that the individuals on the WG are also from a variety of different specialties and have experience with Phase I/II clinical trials in gene therapies and cell therapies.

Closing Remarks

Dr. Coots said that this was a wonderful meeting for him as CCRHB Chair, and he especially acknowledged Dr. Gallin's presentation about the CC history. Hearing the history and reflecting on all the accomplishments of the CC was a great way to ground the Board members. With the charter's approval, he wished the best of luck to the Pediatrics WG and said that the Board looked forward to its report.

The 2023 CCRHB meeting dates are February 17, June 16, and October 20.

Adjournment

Dr. Coots adjourned the meeting at 12:12 p.m.

/ Norvell Coots /_____

Norvell Coots, M.D.

Chair, NIH Clinical Center Research Hospital Board

President and CEO, Holy Cross Health

/ Lawrence A. Tabak /_____

Lawrence A. Tabak, D.D.S., Ph.D.

Executive Director, NIH Clinical Center Research Hospital Board

Performing the Duties of the Director, NIH

Abbreviations and Acronyms

AAV9	adeno-associated virus serotype 9
ACD	Advisory Committee to the Director
ADC	average daily census
AI/ML	artificial intelligence/machine learning
API	application programming interface
ARPA-H	Advanced Research Projects Agency for Health
CC	Clinical Center
CCND	Clinical Center Nursing Department
CCRHB	Clinical Center Research Hospital Board
CDC	Centers for Disease Control and Prevention
CEO	chief executive officer
CIT	Center for Information Technology
CNS	central nervous system
CSF	cerebrospinal fluid
DDIR	Deputy Director for Intramural Research
DEIA	diversity, equity, inclusion, and accessibility
ESI	early-stage investigator
FDA	U.S. Food and Drug Administration
FIRST	Faculty Institutional Recruitment for Sustainable Transformation

FMEA	failure mode and effects analysis
FY	fiscal year
HBCUs	historically Black colleges and universities
HHS	U.S. Department of Health and Human Services
HIV	human immunodeficiency virus
HSIs	Hispanic-serving institution
HTLV-III	human T-lymphotropic virus type III
ICs	Institutes and Centers
ICU	intensive care unit
IRB	Institutional Review Board
IRP	Intramural Research Program
IV	intravenous
LSD	lysosomal storage disorder
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NHGRI	National Human Genome Research Institute
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIH	National Institutes of Health

OHSRP	Office of Human Subjects Research Protections
OPA	Office of Portfolio Analysis
OPSCQ	Office of Patient Safety and Clinical Quality
ORSC	Office of Research Support and Compliance
PAG	Patient Advisory Group
PET	positron emission tomography
PI	principal investigator
PICC	peripherally inserted central catheter
PPG	Pediatric Planning Group
STARS	Safety Tracking and Reporting System
STRIDES	Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability
TCUs	Tribal colleges and universities
WG	Working Group