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National Institutes of Health

Twentieth Meeting of the Clinical Center Research Hospital Board

April 1, 2022

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*Absent

Executive Summary

The Clinical Center Research Hospital Board (CCRHB) of the National Institutes of Health (NIH) convened its 20th meeting via videoconference on April 1, 2022. The meeting was webcast live and open to the public. A video recording of the meeting is available online.

Laura Forese, M.D., Executive Vice President and Chief Operating Officer, NewYork–Presbyterian Hospital, and Chair, CCRHB, called the meeting to order at 9:00 a.m. ET. Julie A. Freischlag, M.D., Dean, Wake Forest University School of Medicine, was absent.

Dr. Forese acknowledged that this would be the final meeting for Ellen Berty, patient, special education teacher, book author, and former NIH research participant. Dr. Forese also announced that she, Ruth Brinkley, MSN, and Richard P. Shannon, M.D., Chief Quality Officer, Duke Health, would be leaving the CCRHB later in 2022, and William Hait, M.D., Ph.D., Global Head of External Innovation, Johnson & Johnson, could no longer serve on the Board due to other commitments.

Lawrence A. Tabak, D.D.S., Ph.D., Acting Director, NIH, thanked Ms. Berty for her service to the CCRHB. Dr. Tabak also welcomed several new *ad hoc* experts to the Board: David Baum, patient, Clinical Center Patient Advisory Group, who was unable to attend; David C. Chin, M.D., M.B.A., Distinguished Scholar, Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health; Antoinette Royster, patient, Clinical Center Patient Advisory Group; and Craig Samitt, M.D., M.B.A., Founder and Chief Executive Officer, ITO Advisors.

Dr. Tabak acknowledged the departure of Francis Collins, M.D., Ph.D., as NIH Director. Dr. Tabak will serve as Acting Director until a new NIH Director is nominated by the President and confirmed by the Senate. In addition to the Acting Director, there are several other acting leadership members. Tara A. Schwetz, Ph.D., is the Acting Principal Deputy Director; Courtney F. Aklin, Ph.D., is the Acting Associate Deputy Director; and Lyric Jorgensen, Ph.D., is the Acting Associate Director for Science Policy.

Dr. Tabak also shared updates about the NIH budget. The Fiscal Year (FY) 2022 Omnibus Appropriations Bill was passed, and NIH received generous increases in funding for its overall budget and other specific research areas. The FY 2022 Omnibus Appropriations Bill also included $1 billion for the establishment of the Advanced Research Projects Agency for Health (ARPA-H). Although ARPA-H is an autonomous organization, NIH will provide administrative and operational support. Congressional hearings for the FY 2023 budget will be in May, and Dr. Tabak was optimistic about continued strong funding for NIH research.

James Gilman, M.D., Chief Executive Officer, NIH Clinical Center, shared that the Clinical Center Nursing Department won the 2021 Press Ganey Award for National Database of Nursing Quality Indicators (NDNQI), which recognizes excellence in patient safety. The Clinical Center is actively recruiting for several leadership vacancies, including a Chief Nursing Officer, Chief Financial Officer, Chief of Pharmacy Department, and Chief of the Office of Clinical Research Training and Medical Education.

Although other parts of the NIH campus are relaxing their coronavirus disease 2019 (COVID-19)–related policies, Dr. Gilman said that the Clinical Center continues to focus on patient and

staff safety through mask mandates and testing. The average daily census for 2021 was well below the 3-year average, but there have been increases in outpatient visits and new patients visiting the Clinical Center. Dr. Gilman is hopeful that Clinical Center operations will continue to increase over the course of the next few months.

Dr. Gilman shared updates on the Clinical Center's efforts to focus on improving diversity, equity, inclusion, and accessibility (DEIA). The Clinical Center has conducted listening sessions, released surveys, and formed a DEIA advisory committee and continues to assess workforce demographics. The Clinical Center also recently submitted its racial and ethnic equity plan to NIH leadership.

David Lang, M.D., M.P.H., Director, NIH Clinical Center Office of Patient Safety and Clinical Quality, presented metrics from the Clinical and Safety Performance Metrics Executive Dashboard that indicate consistent strong performance in infection control, nursing care, and employee safety.

H. Clifford Lane, M.D., Deputy Director of Clinical Research and Special Projects; Director, Division of Clinical Research; and Clinical Director, National Institute of Allergy and Infectious Diseases, provided a comprehensive update on the state of the COVID-19 pandemic, including the latest research related to the disease's pathogenesis, diagnosis, treatment, and prevention. Dr. Lane highlighted several NIH-led efforts, including the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) trials, the COVID-19 Treatment Guidelines, the OpenData Portal on SARS-CoV-2 Variants and Therapeutics from the National Center for Advancing Translational Sciences, and emerging research on the post-acute sequalae of COVID-19 being conducted at the Clinical Center.

Marilyn Farinre, Pharm.D., M.B.A., Service Chief, Pharmacy Operations, Pharmacy Department, Clinical Center, shared an update on the Permanent Pharmacy Placement Project. The inpatient, unit dose, and intravenous admixture units of the pharmacy are being renovated after an inspection by the U.S. Food and Drug Administration found the space to be noncompliant. The new pharmacy space will feature increased capacity, automation, and electronic documentation for safe and efficient workflows. All three units should be operating in the new space by the end of 2022.

Dan Wheeland, PE, Director, NIH Office of Research Facilities, presented on Clinical Center construction and renovation projects that are planned or underway, including the initial planning stages for the long-awaited Surgery, Radiology, and Laboratory Medicine Building. All of these construction projects will increase patient safety and expand research facilities.

W. Marston Linehan, M.D., Chief of Urologic Surgery and the Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute, closed the meeting with a historical perspective of kidney cancer research at the Clinical Center. More than 30 years of research at the Clinical Center has led to the identification of many sporadic and hereditary kidney cancer genes and enhanced precision treatment and care of kidney cancers. Specifically, foundational research on Von Hippel-Lindau (VHL) syndrome and its associated kidney cancer led to Nobel Prize–winning research. Dr. Linehan's group recently published clinical trial results about a promising treatment option for people with VHL kidney cancer.

The next meeting of the Board will occur on July 15, 2022.

Meeting Summary
Friday, April 1, 2022

Welcome and Board Chair's Overview

Laura Forese, M.D., M.P.H., Executive Vice President and Chief Operating Officer, NewYork–Presbyterian Hospital, and Chair, Clinical Center Research Hospital Board (CCRHB)

Dr. Forese called the meeting to order at 9:00 a.m. ET and checked attendance, welcoming the new members of the CCRHB.

Dr. Forese acknowledged that this was the last board meeting for Ellen Berty, who has served on the CCRHB since its inception. Ms. Berty has been a critical voice for the patient and created joy with her fabulous costumes. Ms. Berty said that she learned a great deal from this experience and thanked the Board for their work on behalf of patients everywhere.

Dr. Forese announced that she, Ruth Brinkley, MSN, and Richard P. Shannon, M.D., would also be leaving the board in 2022. Their departures will be staggered to facilitate a smooth transition, but all plan to attend the July CCRHB meeting. Additionally, William Hait, M.D., Ph.D., had to withdraw as an *ad hoc* Board member due to other commitments. Dr. Forese thanked him for his service to the CCRHB.

National Institute of Health (NIH) Director's Remarks

Lawrence A. Tabak, D.D.S., Ph.D., Acting Director, National Institutes of Health (NIH), and Executive Director, CCRHB

Dr. Tabak thanked Ms. Berty for her contributions to the CCRHB. As a founding member of the Board and a former NIH research participant, she has provided important insight over the years. Dr. Tabak also shared the thanks of Francis S. Collins, M.D., Ph.D.

Dr. Tabak acknowledged the new CCRHB members. Craig Samitt, M.D., M.B.A., is the managing director of ITO Advisors and a nationally recognized thought leader on industry transformation, care delivery, and healthcare policy. David Chin, M.D., M.B.A., is the Director of Executive Education and Co-Director of the M.P.H./M.B.A. Program at the John Hopkins Bloomberg School of Public Health. Dr. Chin also serves as Chair of the Board of Directors for the National Committee of Quality Assurance.

The CCRHB also welcomes two new patient representatives. Antoinette Royster is a civic-minded activist who has participated in many studies at the Clinical Center and has served on the NIH Clinical Center Patient Advisory Group since 2005. David M. Baum, PMP, was not able to attend, but he is the Managing Director of QX Group, Ltd., and has extensive public- and private-sector experience. The CCRHB is fortunate to have these new members serve on the Board and share their unique insights.

Leadership Updates at NIH

Dr. Tabak said that Dr. Collins stepped down as NIH Director after serving 12 years under multiple presidential administrations. Dr. Collins planned to focus on his laboratory research but is now serving as the acting science adviser to the President.

Although the timing is uncertain, the President will nominate a new, permanent NIH Director, who will then have to be confirmed by the Senate. NIH leadership is confident that the President will nominate a spectacular candidate, and once that person is confirmed, leadership looks forward to working with the new Director to implement their agenda.

During this interim period, Dr. Tabak is serving as Acting Director and is supported by three leaders who have stepped into acting roles. Tara A. Schwetz, Ph.D., is the Acting Principal Deputy Director, returning to NIH after serving in the White House Office of Science and Technology Policy (OSTP) to manage early planning of the Advanced Research Projects Agency for Health (ARPA-H). Courtney F. Aklin, Ph.D., took on Dr. Schwetz's role as the Acting Associate Deputy Director. Lyric Jorgensen, Ph.D., is now the Acting Associate Director for Science Policy, since Carrie Wolinetz, Ph.D., is on detail at OSTP. Dr. Tabak expressed his gratitude for these three leaders.

Also, on March 1, the Foundation for the National Institutes of Health (FNIH) announced the appointment of Julie Louise Gerberding, M.D., M.P.H., as the Chief Executive Officer (CEO) of FNIH. She is the former Director of the Centers for Disease Control and Prevention (CDC) and current Chief Patient Officer and Executive Vice President, Population Health and Sustainability at Merck. Dr. Gerberding currently sits on the Board of Directors and Governance at FNIH and will begin her role as CEO on May 16.

Update on the NIH Budget

With the upcoming mid-term elections, there is some uncertainty related to the fiscal year (FY) 2023 budget. The FY 2022 Omnibus Appropriations Bill was passed recently, and NIH is extremely grateful to Congress for their support. The total NIH budget for FY 2022 is $45.18 billion, which is an increase of $2.24 billion (5.2%) from FY 2021. The general increase for the Institutes and Centers (ICs) was 3.4%, and specific areas of research received generous additional funding, including Alzheimer's disease ($289 million), cancer ($150 million), opioid use disorder ($75 million), health disparities ($50 million), and the Brain Research Through Advancing Innovative Neurotechnologies® (BRAIN) initiative ($60 million).

The FY 2022 Omnibus Appropriations also included $1 billion to establish ARPA-H within the Department of Health and Human Services (HHS). The secretary of HHS recently announced that he would use his authority to transfer ARPA-H authorities and funds to NIH. Although ARPA-H is an independent entity, NIH will provide administrative and operational support to ensure a rapid and efficient startup of the agency. The ARPA-H Director will be appointed by the President without Senate confirmation and will report to the Secretary of HHS, who is expected to appoint an Interim Director to facilitate the launch of ARPA-H.

Soon after the FY 2022 Omnibus Appropriations Bill was passed, the President released his proposed FY 2023 budget. Dr. Tabak and selected IC Directors will participate in appropriations hearings for NIH at the House of Representatives on May 11 and the Senate on May 18.

Finally, Dr. Tabak congratulated the Clinical Center on its recent award for the new Surgery, Radiology, and Laboratory Medicine (SRLM) Building. The work for this project predated the CCRHB, so it has been in the works for a long time, and it is very exciting to see it come to fruition. The build-out date is set for 2028.

Discussion

Dr. Forese echoed Dr. Tabak's excitement for the SRLM Building.

Stephanie Reel, M.B.A., asked about the reasoning for ARPA-H being separate from NIH. Dr. Tabak said that in listening sessions with stakeholders, there was a call for ARPA-H to be unencumbered and independent; however, NIH can support a rapid and robust start for the agency. Dr. Schwetz said that many operational and structural functionalities need to be built when starting a new agency, and NIH's scientific knowledge and expertise can be leveraged during this process. One of the fundamental tenets of ARPA-H is autonomy, so its separation from NIH but connection to the Secretary for HHS supports this tenet. This set-up is similar to those of the Advanced Research Projects Agency–Energy, which is part of the Department of Energy, and the Defense Advanced Research Projects Agency, which is part of the Department of Defense.

NIH Clinical Center Chief Executive Officer Update

James Gilman, M.D., Chief Executive Officer, Clinical Center

Dr. Gilman welcomed NIH colleagues participating in the meeting via Zoom, including Clinical Center leadership executives:

- Colleen M. Hadigan, M.D., M.P.H., Chief Medical Officer, Clinical Center
- Pius Aiyelawo, M.P.A., Chief Operating Officer, Clinical Center
- Barbara Jordan, D.N.P., RN, NEA-BC, Acting Chief Nursing Officer, Clinical Center

Dr. Gilman also acknowledged Natascha Pointer and Patricia Piringer for their work to coordinate the CCRHB meeting.

CCRHB Transitions

Dr. Gilman welcomed Mr. Baum, Dr. Chin, Ms. Royster, and Dr. Samitt to the CCRHB as ad hoc experts. Dr. Gilman thanked Dr. Chin for his help with recruiting Dr. Samitt to be considered for the Board.

Although Ms. Berty is leaving the CCRHB, she will continue to serve on the Clinical Center Patient Advisory Group.

Ruth Williams-Brinkley, M.S.N.-Adm., is leaving the Board in the next few months. Her contributions to the board as a nurse remain invaluable and there are efforts to find a new Board member with a nursing background. Dr. Gilman has been in contact with a nurse executive of a hospital and hopes to announce this new Board member at the July meeting.

Awards

Dr. Gilman said that Ms. Williams-Brinkley and Dr. Forese were named as the Top Women Leaders in Healthcare 2022 by Modern Healthcare.

The Clinical Center was one of six hospitals to win the 2021 Press Ganey Award for National Database of Nursing Quality Indicators (NDNQI). The Clinical Center exceeded the mean in 17 indicators for patient safety and was acknowledged as the top teaching hospital. The award went on tour throughout the Clinical Center so that the nurses and staff who contributed to this achievement could celebrate.

The Clinical Center was well represented at the 2021 NIH Director's Awards. There were 15 awards honoring 155 Clinical Center employees, including 5 individual awardees and 150 group awardees.

The Annual Clinical Center CEO Awards Ceremony in December 2021 recognized more than 700 Clinical Center employees with 111 awards, 43 individual awards and 68 group awards.

The Part of Something Bigger Award, a new award developed by HHS, is given to HHS staff members who contribute to the department's goals outside the workplace. Two Clinical Center employees were recognized for their volunteer work at mass vaccination sites for coronavirus disease 2019 (COVID-19) COVID-19 vaccines.

Clinical Center Staffing Update

Dr. Gilman said that the Clinical Center is actively recruiting for several leadership vacancies:

- Chief Nurse Officer
- Chief Financial Officer
- Chief of Pharmacy Department
- Chief, Office of Clinical Research Training and Medical Education

The Chief of Materials Management and Environmental Services and the Designated Institutional Official for the Accreditation Council Graduate Medical Education positions were recently filled.

As more NIH staff return to campus, Clinical Center leadership is also working to update teleworking policies for staff. Although most of the Clinical Center's work occurs in person, some staff have the option of working remotely.

Event Updates

Dr. Gilman hosted the quarterly Clinical Center Town Hall on January 25, 2022. The format of this town hall, which was changed to include more members of executive leadership in the presentations of length-of-service awards, CC overview and highlights, and Q&A, was received well. The next town hall will focus on diversity, equity, inclusion, and accessibility (DEIA) issues.

The Clinical Center co-hosted Rare Disease Day with the National Center for Advancing Translational Sciences (NCATS) on February 28, 2022. Although the event was again held

virtually, it was a success. Several members of the Rare Disease Congressional Caucus attended the event.

Updates: Office of Communications, Media Relations, and Patient Recruitment (OCMR)

Dr. Gilman showed examples of how OCMR is leveraging social media and other platforms to advertise Clinical Center studies and find people who may be interested in participating in these studies. OCMR is using targeted ads on Facebook, Instagram, and Nextdoor to reach people who may benefit from these studies. These are low-cost efforts that can target both narrow populations (e.g., specific wards in Washington, D.C.) or a broader group of people (e.g., multiple states and countries). There has been great engagement with the Facebook ads, and OCMR is tracking people who contact the Clinical Center to participate in studies as a result of these ads. Other outreach efforts have included printing information about the Clinical Center on pharmacy bags at local pharmacies and on signs at local shopping centers. All of these efforts are aimed at sharing the Clinical Center's presence and efforts with the community.

Average Daily Census (ADC)

The Clinical Center has operated at much lower capacity during the course of the COVID-19 pandemic. The ADC for 2021 was well below the 3-year average, and the usual drop in the number of patients in December was much lower due to the Omicron variant. There have been some improvements: There was a 20% increase in outpatient visits and a 10% increase in new patients between 2021 and 2022. Also, the cancer and bone marrow transplant units are very busy. In March 2022, the operating rooms were the busiest they have been in many months, and these increases are expected to continue in the summer months.

Before the COVID-19 pandemic, the Clinical Center did not use telehealth visits. In March 2020, the Health Information Management Department and the Department of Clinical Research Informatics collaborated to develop a telehealth platform and related policies. There were more than 1,200 telehealth visits per month at some points, but now the average is 800 to 1,000 telehealth visits per month. This platform is an important way to continue research and serve patients during the COVID-19 pandemic.

Current Clinical Center Response to COVID-19

Dr. Gilman explained that the Clinical Center still has more stringent COVID-19–related restrictions than other places on campus, because many Clinical Center patients are immunosuppressed or immunocompromised. Some restrictions have been eased, such as travel restrictions and masking outside Building 10. Other restrictions, such wearing a mask in the building and being screened for COVID-19, have not been lifted. By following the COVID-19 related restrictions, CC staff have been able to provide safe patient care while keeping themselves and each other safe.

The Hospital Epidemiology Service at the Clinical Center and the Occupational Medical Service within the Office of Research Services at NIH have worked to together to conduct careful contact tracing throughout the COVID-19 pandemic. Dr. Gilman was proud to report that it had been almost 2 years since the last documented case of patient-to-staff transmission of COVID-19, and there have been no cases of staff-to-patient transmission at the Clinical Center.

The Clinical Center has screened almost 3 million people for COVID-19 and conducted more than 165,000 asymptomatic tests. During the Omicron surge, there was 1 positive asymptomatic case per every 20 tests; that has now fallen to 1 positive test per every 700 to 1,000 asymptomatic tests.

Diversity, Equity, Inclusion, and Accessibility Program

Dr. Gilman said that DEIA is an issue not limited to the Clinical Center; rather, DEIA is a major focus throughout the NIH. The Clinical Center has launched a comprehensive DEIA program that includes an advisory committee that reports to the Clinical Center CEO. All DEIA activities, including recent Black History Month and Women's History Month activities, are shared on a dedicated page on the Clinical Center's Intranet site.

As part of its DEIA efforts, Clinical Center leadership regularly assesses workforce demographics and administered a survey to find areas where there are gaps in DEIA. The survey was followed by listening sessions to gain more insights on perceptions versus reality on the Clinical Center's progress toward a more equitable workplace. The goal is to create initiatives to address the biggest issues with DEIA at the Clinical Center.

Leadership has also submitted the Clinical Center's racial and ethnic equity plan, which will be reviewed by Lawrence A. Tabak, D.D.S., Ph.D., the NIH Acting Director, and Tara A. Schwetz, Ph.D., the Acting NIH Principal Deputy Director. It is a living document that can be updated over time based on specific DEIA needs. The CCRHB will hear more detailed updates on this report and other DEIA efforts at the Clinical Center at a future meeting.

In 2019, the Clinical Center released The NIH Clinical Center at 65: Strategic Plan. The CCRHB will review the strategic plan during the July meeting, which will be a great opportunity for the new members to learn more about the Clinical Center's activities and provide feedback on what should be featured in the next iteration of the strategic plan.

Discussion

In response to Ms. Royster's question about remote clinical studies, Dr. Gilman said that these studies do not require the patient to come to the Clinical Center. These studies usually involve surveys and might require bloodwork, which could be collected through a commercial provider. All remote clinical study participants must undergo careful screening and complete a consent process.

Dr. Shannon suggested that demographic assessments of the Clinical Center workforce should be categorized by job level to understand any diversity issues for specific jobs, particularly senior positions. Dr. Gilman agreed and said that Clinical Center leaders are assessing demographics based on job level and series.

Dr. Shannon asked how pipeline programs (e.g., partnerships with Historically Black Colleges and Universities [HBCUs]) have translated into workforce diversity at the Clinical Center. Dr. Gilman said that although pipeline initiatives are important, they are not enough. NIH and the Clinical Center need to focus on their relationship with HBCUs and other minority-serving institutions and evaluate whether the outreach efforts lead to people applying and being accepted for jobs at the Clinical Center. The Clinical Center has baseline data about demographics, but more effort is needed to understand which actions lead to improved workforce diversity. The

answer is not to create more pipeline initiatives but instead to make sure existing initiatives are working well. John I. Gallin, M.D., added that the focus on diversity spans across the intramural research program at NIH. The Clinical Center has established regional partnerships with nine institutions, including Howard University. Several ICs, including the National Cancer Institute, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Institute of Allergy and Infectious Diseases (NIAID), and the National Heart, Lung, and Blood Institute (NHLBI), have established programs that are bringing a whole new spectrum of researchers to NIH, ranging from undergraduate to medical students to tenure-track investigators. The CCRHB will hear more about these efforts at a future meeting.

Dr. Samitt asked whether lower occupancy will be a new normal at the Clinical Center. Dr. Gilman said that the Clinical Center never surged in patients during the pandemic, because it never took on COVID-19 patients the way community hospitals did, except in December 2020 when Maryland hospitals were at capacity. The decrease in occupancy during the pandemic was caused by limitations on travel. Half of the research protocols at the Clinical Center are natural history protocols, and many patients travel to the Clinical Center from across the country and the world. Many patients can delay their travel plans until the pandemic is over. The Clinical Center occupancy rate is never more than 80% to 85% of beds, but the ADC should return to the 3-year average over the course of the next year or so.

Clinical and Safety Performance Metrics

David Lang, M.D., M.P.H., Director, Office of Patient Safety and Clinical Quality, Clinical Center

Dr. Lang thanked the Clinical Center staff for their efforts to reach the goal of zero harm.

Infection Control

Dr. Lang reported on several metrics related to infection control:

- The hand hygiene metric is consistently in the 90-95% range; it is based on observations, not self-reports. Trained staff throughout the organization conduct "secret shopper" observations.
- The rates of central-line–associated bloodstream infections (CLABSIs) are measured as numbers per 1,000 line days. After there was a reduction in CLABSIs in the previous five quarters, there was an increase in the most recent two quarters; however, the number of events remains very low. For every CLABSI, the nursing and hospital epidemiology service investigates the event, determines whether there are trends, and uses the opportunity to remind staff about the best practices of line care.
- The rate of CLABSIs in the intensive care unit (ICU) is more variable, because the ICU has a smaller patient population; however, the number remains low. The benchmark is based on the National Healthcare Safety Network ICU benchmark, which will be updated soon for 2022.
- Catheter-associated urinary tract infections (CAUTIs) in the ICU are at zero and have remained at zero for two quarters. Surgical oncology CAUTIs have been at zero for the past two quarters.

- Surgical site infections were compared to the average for the Clinical Center for 2018–2019. The numbers remain low and have stayed around the comparison average.

Nursing Quality Metrics

Dr. Lang reviewed the nursing quality metrics and expressed his pride for the nursing department for their work to win the National Database of Nursing Quality Indicators (NDNQI) award.

- Inpatient falls are measured per 1,000 patient days. The rates remain at or below the NDNQI benchmark. The Clinical Center is implementing strategies to reduce inpatient falls further, including using a bedside mobility assessment tool.
- Pressure injury prevalence has varied above and below the NDNQI benchmark. No stage 3 or 4 pressure injuries have occurred for many quarters.
- The barcoding system helps eliminate errors with medication administration. The goal is to use barcoding 100% of the time, but the rate is usually around 99%. Barcoding is not always feasible in a few parts of the Clinical Center, but extra care is taken to ensure correct medication administration.

Emergency Response

Dr. Lang explained that "Code Blue" is called for all types of emergencies, including for visitors and employees. The number of Code Blues called in 2021 was similar to the number called in 2019. Half were called for patients, a third were for outpatients, and the rest were for visitors and employees. Most codes are for acute emergencies and stable events, such as falls. Only 15% of these are for cardiac arrest events. After a Code Blue, most people stay on unit; approximately 25% are transferred to the ICU. Those transferred to an outside hospital are usually visitors or employees who need additional care.

Rapid Response Team

Dr. Lang said that the Rapid Response Team (RRT) is called if the floor team or unit need additional help. After a rapid response, most patients remain on unit. A smaller number are admitted to an inpatient unit, and about 15% of patients are admitted to the ICU. Each Code Blue and RRT call is reviewed by a multidisciplinary group to assess any trends or process issues.

Blood and Blood Product Use

Dr. Lang said that the goal crossmatch-to-transfusion ratio is 2 or less to ensure that blood is not held unused in reserve when it can be used for another patient. The Clinical Center is consistently below that goal ratio, and the ratio has remained stable over the course of the year.

The percentage of transfusions associated with transfusion reactions has consistently been 1% or lower. A majority of these events are classified as fever without hemolytic reaction, and there are no reports of severe reactions.

Blood bank specimens are used for crossmatching. The percentage of specimens that are deemed unacceptable due to labeling problems or hemolysis is currently around 1.75%, well below the threshold of 3%. Unacceptable blood samples are discarded, and new samples are drawn.

Clinical Documentation

Dr. Lang said that the Clinical Center's patient record completion delinquency rate at greater than 30 days post discharge is around 5% to 6%, much lower than the Joint Commission benchmark of 50%.

"Agent for" orders countersignature compliance has been consistently around 95%.

"Do not use" abbreviation adherence is around 95%.

The Clinical Center goal for accuracy of record coding is above 90%, and the rate has remained around 95%.

Employee Safety

Dr. Lang said that during the last CCRHB meeting, there was a request to present employee safety data with benchmarks against other U.S. hospitals. The Clinical Center's data were compared against combined data over the past several years from the Bureau of Labor Statistics. Dr. Lang shared several employee safety metrics:

- Total reportable cases and other reportable cases of occupational injuries or illnesses were frequently below the national average for a hospital of the CC's size.
- The days away, restricted, or transferred (DART) is a combined metric of the days of job transfer, restriction and the days away from work. Most DART are related to musculoskeletal injuries. One initiative to address this issue is the bedside mobility assessment tool; another is the use of an air mattress system to move patients from bed to bed, used as much as possible to keep patients and employees safe from injury.

Discussion

Dr. Forese said that Paul H. O'Neill was one of the original board members who was very focused on team member safety, so it is great to see a focus on these data.

Ms. Royster remarked on how impressive it is that the Clinical Center has consistently maintained a 0% CAUTI rate. Dr. Lang said that this rate was low thanks to certain nursing practices.

Dr. Forese mentioned the recent news story about a nurse who was convicted for a medication error at Vanderbilt University and asked how the Clinical Center is supporting its nurses during this time. Dr. Jordan said that statements of support for nurses from the Maryland Nurses Association, the American Nursing Association, and the leadership at the Clinical Center were shared with nursing staff. Although staff responded positively to these statements, there is still concern that nurses will not report mistakes due to fear of retaliation. The Clinical Center is focused on a culture of safety, fairness, and open discussion so that reports can be handled properly while staff are still supported. Steven I. Goldstein, M.H.A., shared that his institution has created a nursing group that reviews events in such a way that nurses still feel supported. In the chat, Dr. Shannon, M.D., shared an article by David Marx that unpacks the legal and just-culture issues in the Vanderbilt case.

Ms. Reel highlighted how the increased levels of fatigue among all healthcare workers could have safety implications and asked whether the Clinical Center staff is experiencing this fatigue.

Dr. Jordan said that fatigue is an issue for staff, and the Clinical Center is making every effort to monitor issues related to fatigue and provide support or solutions (e.g., monitoring shift lengths and frequency). Additionally, the crisis hotline for staff was recently reopened. Dr. Lang added that there are many processes in place to help staff avoid errors, but any errors that occur are closely assessed for any process problems, compliance issues, or staff issues, such as the perceived need for rushing or feelings of fatigue.

Dr. Shannon asked whether the Clinical Center has been affected by staff turnover or shortages, which can also lead to safety issues. Dr. Jordan said that like many U.S. hospitals, the Clinical Center is experiencing greater staff turnover. Additionally, the Clinical Center has had difficulty hiring contract staff, because they are being offered higher pay at hospitals in areas hit hard by the pandemic. Another issue is that patients who come to the Clinical Center have very high acuity and complex issues, which can lead to fatigue. But there should also be considerations of COVID-19–related stressors outside of work, such as homeschooling. Dr. Lang added that COVID-19 policies at the Clinical Center, such as staff not being allowed to eat together or patients not being allowed to have visitors, could also be causing stress. Dr. Gilman said that the federal healthcare system makes it easy for staff to leave quickly; getting staff onboarded takes longer. There is also stress among researchers who are anxious to restart their clinical trials and are feeling the pressure of performing for their tenure-track positions. The Clinical Center is doing its best to balance taking care of as many patients as possible and maintaining safety and continues to emphasize that seeking help is a sign of strength.

Novel COVID-19 Update

H. Clifford Lane, M.D., Deputy Director of Clinical Research and Special Projects; Director, Division of Clinical Research; Clinical Director, National Institute of Allergy and Infectious Diseases

Organizational Structure

Dr. Lane highlighted staffing changes on the COVID-19 response team at the White House. Andy Slavitt, M.B.A., recently left his position as the White House Senior Advisor on the COVID-19 response. White House Coronavirus Response Coordinator Jeff Zients will be leaving soon and will be replaced by Ashish Jha, M.D., M.P.H., the current Dean of Brown University's School of Public Health. His appointment was scheduled to begin April 5.

Operation Warp Speed was established under a memorandum of understanding (MOU) between the Department of Health and Human Services (HHS) and the Department of Defense. The MOU expired on December 31, 2021. On January 1, 2022, Operation Warp Speed became the HHS Coordination Operations and Response Element, which is led by Dawn O'Connell, J.D., at the Office of the Assistant Secretary for Preparedness and Response and with Jason Roos, Ph.D., as Chief Operating Officer. David Kessler, M.D., remains a key player as the HHS Chief Science Officer for COVID-19.

On March 2, the White House released the National COVID-19 Preparedness Plan. The plan features four main elements: Protect against and treat COVID-19, prepare for any new variants, prevent economic and educational shutdowns, and continue to lead the effort to vaccinate the

world and save lives. The funding outlined in this plan did not pass in Congress, so it is uncertain which elements of this plan will come to fruition.

Pathogenesis

Dr. Lane explained that the conventional wisdom about the course of COVID-19 is that the early phase of infection is driven by the virus and is best treated by antivirals. Later phases are driven by the immune response to the virus, leading to inflammation. This part of the disease course is treated with immunomodulatory strategies. Additionally, anti-coagulation treatments are needed throughout the disease course.

Emerging data suggest that the virus plays a role throughout the course of infection. Researchers collected serum from hospitalized COVID-19 patients who were part of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)-3 trial. They measured the amount of circulating virus in the serum using a nanotechnology developed by Quanterix Technology that uses small magnetic beads with antibodies for the core protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As disease severity increases (e.g., with progressive levels of oxygen support required), the plasma levels of antigen increase. Although it is unclear how this increased level of virus relates to viral replication, these data suggest that antiviral therapies may be needed throughout the disease course, especially as immunosuppression is needed to treat inflammation.

The most recent SARS-CoV-2 variant is the Omicron variant. Although it has many different changes from the Delta variant, Omicron does not appear to be as pathogenic. The CDC has a website that shows the most dominant SARS-CoV-2 variants in the U.S. population over time and projections for the next 2 weeks. The end of 2021 had a mixture of Delta and Omicron, but Omicron became the most prevalent variant within a month. Now, the BA.2 Omicron variant is quickly becoming the dominant variant. These data are important because they help us understand which monoclonal antibodies will be the most effective against new variants. NCATS supports a website that compiles data on the efficacy of various treatments, including vaccines, antibody treatments, antivirals, and convalescent plasma and serum, against different variants. Sotrovimab, the antibody with the best efficacy against the Omicron variant, does not appear to have efficacy against the BA.2 variant. Bebtelovimab is the only antibody available with efficacy against the BA.2 variant.

In France, COVID-19 cases are increasing due to the BA.2 variant; however, there is no evidence that a similar surge in cases will occur in the United States, likely due to differing epidemiology and susceptibility between the French and U.S. populations.

Diagnostics

Dr. Lane said that reverse transcription polymerase chain reaction (RT-PCR) test remains the most sensitive tool for diagnosing COVID-19, but a person can test positive for COVID-19 by RT-PCR for a long time after infection. RT-PCR has also been used to identify SARS-CoV-2 variants and subvariants through amplification of the S-gene. Antigen testing is less sensitive, but it is easily done at home. Both diagnostic methods are available under Emergency Use Authorization (EUA), but they need approval from the U.S. Food and Drug Administration (FDA) to continue to be used after the public health emergency is lifted.

Therapeutics and Treatment Guidelines

Dr. Lang explained that the NIH established the ACTIV clinical trial infrastructure to test therapeutic strategies for ambulatory and hospitalized patients. There are several ACTIV trials with different treatment focuses:

- ACTIV-1, -3, -4a, and -5: host-directed therapies and antivirals in hospitalized patients
- ACTIV-2: antiviral therapies in ambulatory patients
- ACTIV-6: repurposed drugs in ambulatory patients (e.g., ivermectin, fluvoxamine)

There are extensive, rapidly changing guidelines for COVID-19 treatments. It is extremely difficult for anyone to remain current with the latest knowledge, so NIH has created a website that shares the latest information for treating COVID-19. This website was created as a directive from HHS on March 20, 2020, and the first guideline release occurred on April 21, 2020. Since then, there have been 48 updates and more than 34 million page views.

The guidelines provide two types of rating: strength of recommendation (strong, moderate, or weak) and strength of the evidence (data from robust, randomized controlled trials; data from other trials or observational studies; or expert opinion). There are different guidelines for ambulatory and hospitalized patients, and each set of guidelines is further divided based on patient disposition. Dr. Lang shared some treatment guideline examples:

- Ambulatory patients with mild to moderate COVID-19 who are at risk for severe disease progression should be treated with Paxlovid (a combination of nirmatrelvir and ritonavir).
- Bebtelovimab is the most affective monoclonal antibody therapy for the BA.2 variant.
- Ambulatory and hospitalized patients should not be treated with corticosteroids if they do not require oxygen.
- Hospitalized patients who require supplemental oxygen can be treated with a combination of remdesivir, baricitinib, interleukin 6 inhibitors (e.g., tocilizumab, sarilumab), and corticosteroids (e.g., dexamethasone).

Prevention

Dr. Lane highlighted the six COVID-19 vaccines developed in the United States and their approval status.

- Moderna (mRNA): FDA-approved for age 18 and older
- BioNTech–Pfizer (mRNA): FDA-approved for age 16 and older, EUA for ages 5 to 15
- Johnson & Johnson (adenovirus): EUA for age 18 and older
- AstraZeneca (adenovirus): EUA request has not been submitted
- Sanofi-GSK (recombinant protein and adjuvant): EUA request submitted February 2022
- Novavax (recombinant protein and adjuvant): EUA request submitted January 2022

Dr. Lane noted that the two recombinant protein and adjuvant vaccines will likely be used in booster regimens if their EUAs are approved.

There are also 10 vaccines approved by the World Health Organization: two protein subunit vaccines, two mRNA vaccines, three adenovirus-based vaccines, and three inactivated virus vaccines.

There is compelling data showing the efficacy of the vaccines at preventing hospitalizations. According to the CDC, when looking at age-adjusted rates of COVID-19–associated hospitalizations by vaccination status in U.S. adults age 18 and older between October 2021 and January 2022, there were 9.8 per 100,000 hospitalizations among fully vaccinated (i.e., one Johnson & Johnson shot or two mRNA shots) with an additional or booster dose and 35.2 per 100,000 for fully vaccinated without an additional or booster dose. Among the unvaccinated, the hospitalization rate was 145.1 per 100,000.

Data from a randomized controlled trial conducted by BioNTech–Pfizer show the efficacy of a booster shot at reducing the rate of COVID-19 infection; however, these data were generated prior to the Omicron variant's emergence. Recent data suggest that although it is created toward the ancestral strain of COVID-19, the booster shot does improve immunity against the Omicron variant. Data show increased neutralizing antibody titers 1 and 6 months after the booster. Data on neutralizing antibody titers also show that any combination of BioNTech–Pfizer, Moderna, and Johnson & Johnson vaccines as the primary vaccine and the booster vaccine will create a strong immune response.

Although data clearly support that COVID-19 vaccines are safe and effective, there are several unanswered questions, such as the duration of protection from infection, symptoms, hospitalizations, and death. It is also unclear what the best regimen is for children under 5 years old, but those data are still being reviewed.

On March 29, FDA authorized a fourth mRNA dose (a second booster) for individuals who are 50 and older at least four months after their first booster dose. This authorization also covers immunocompromised people who are 12 and older and want to receive the BioNTech–Pfizer booster and immunocompromised people who are 18 and older who want to receive the Moderna booster. The supporting safety evidence on the BioNTech–Pfizer second booster is from 700,000 people, whereas the Moderna safety data are from 120 people; however, the data clearly show that neutralizing antibody titers increase after the second booster.

A nonrandomized study from Israel was conducted over a 40-day period and followed 500,000 individuals ages 60 to 100 after they did or did not receive a fourth Pfizer vaccine. The study measured rates of death, but there were many confounders to this study. For example, people who came for a fourth dose had health-seeking behaviors and also took measures to avoid getting infected with COVID-19. Despite these caveats, there were 232 deaths in those who did not receive a fourth dose, with the number at risk ranging from 12,000 to 328,000, and 92 deaths among those who did receive a fourth dose, with the number at risk ranging from 233,000 to 550,000. The adjusted hazard ratio for death was 0.22, which is a remarkable reduction in death based on getting the fourth dose.

Post-Acute Sequelae of COVID-19 (PASC)

Dr. Lane said that PASC is being studied at NIH through the Researching COVID to Enhance Recovery (RECOVER) initiative, co-led by NHLBI and the National Institute of Neurological Disorders and Stroke (NINDS). RECOVER seeks to understand, prevent, and treat PASC,

including long COVID. PASC is also being studied through three protocols at the Clinical Center and supported by NIAID, NINDS, and the Clinical Center.

Dr. Lane highlighted a study supported at the Clinical Center that is being led by Michael C. Sneller, M.D., from NIAID. The study focuses on three cohorts of adults: individuals with a history of COVID-19 and persistent symptoms, those with a history of COVID-19 and no persistent symptoms, and those with no history of COVID-19 but close contact with a COVID-19 survivor. The data collected for this study include individual history and physical, routine labs, markers of inflammation and coagulation, SARS-CoV-2 immunology and virology, mental health evaluation, electrocardiography, echocardiogram, pulmonary function test, and a 6-minute walking test.

Compared with a control group, the symptoms that are most prevalent in COVID-19 survivors are fatigue, dyspnea, anosmia, parosmia, trouble concentrating, headache, memory impairment, trouble sleeping, chest pain or discomfort, and anxiety. Among all COVID-19 survivors, the only differences currently noted between those who develop long-term symptoms and those who do not are female gender and history of an anxiety disorder. Abnormal findings on physical exam or laboratory evaluations were uncommon and were not associated with PASC.

When analyzing the neutralizing antibody titers of these groups, there were large variations in the level of antibodies among unvaccinated COVID-19 survivors, with many not reaching a positive antibody response. Vaccinated COVID-19 survivors had the highest antibody titers. The rate of antibody decline over time after COVID-19 infection was quite variable, so the magnitude and duration of immune response after COVID-19 infection needs to be better studied.

Discussion

Dr. Samitt asked where there is any evidence of any new, emerging COVID-19 variants and whether there is a surveillance mechanism for monitoring new variants. Dr. Lane said that he was not aware of any new variants of concern that are emerging. For example, there was concern about a Delta–Omicron hybrid variant, but that seems to be a RT-PCR artifact and not an actual variant. Omicron is so different from the Delta variant that the hypothesis is that Omicron was mutating within someone for many weeks and then was introduced into the population. As far as surveillance, the NCATS website pulls data from CDC and other groups who are interested in tracking SARS-CoV-2 variants.

Ms. Reel asked whether the United States and the world will be better prepared for the next pandemic after this experience with COVID-19. Dr. Lane said that people are much more aware of how difficult it is to deal with this type of pandemic. There are many efforts to understand the best practices learned during the pandemic, but the actual steps needed to apply these best practices are still in the future.

Permanent Pharmacy Placement Project (P4)—Relocation of the Outpatient and Inpatient Pharmacies

Marilyn Farinre, Pharm.D., M.B.A., Service Chief, Pharmacy Operations, Pharmacy Department, NIH Clinical Center

Dr. Farinre said that in May 2015, for-cause inspection by the FDA led to suspension of activities in the pharmaceutical development section of the Clinical Center pharmacy. In April 2016, the Advisory Committee to the Director and the Clinical Center Working Group released the Red Team report, which found that the Clinical Center pharmacy facilities that were producing sterile products were outdated, and full remediation was recommended. All the pharmacies had to move to temporary spaces: The intravenous admixture unit (IVAU) moved into a temporary space in 2017; the outpatient and unit dose pharmacies moved in 2019. Renovations began in 2021 and are almost complete. The outpatient pharmacy will begin operating out of the newly renovated space on May 2, the unit dose pharmacy will begin operations on May 24, and the IVAU will start operation in fall 2022.

Despite these changes, the pharmacy staff have held true to their mission "to support and conduct clinical research by providing safe, high-quality care, one patient, one medication at a time." P4's goals are to safely continue operations with uninterrupted pharmaceutical care, successfully implement and integrate the pharmacy automation, relocate all supplies and medications as efficiently as possible, and ensure all staff are trained and remain fully engaged.

The renovated pharmacy is more than 10,000 square feet, with separate areas for the outpatient, unit dose, and IVAU pharmacies. Dr. Farinre shared pictures of each of these pharmacies and demonstrated the layout and workflow of each space.

The renovations are compliant with all regulations. Some features of the new pharmacies include:

- A bank-grade vault for controlled medications
- Increased capacity, automation, and electronic documentation for safe and efficient workflows
- Segregated compounding areas
- Engineering controls for processing hazardous and nonhazardous medications
- Carousels for storing medications with barcoding system (one for the outpatient pharmacy, two for the unit dose pharmacy, and two for the IVAU)
- A lounge for pharmacy staff

The outpatient pharmacy is approximately 1,426 square feet and includes many new features, including an automated storage and retrieval system that allows for accurate retrieval, enhanced security, and fulfillment of chain-of-custody requirements for controlled and investigational medications. The outpatient pharmacy also has a robotic dispensing system that automates the filling process and allows pharmacists to spend more time on their clinical duties.

The unit dose pharmacy is approximately 2,300 square feet. It features designated workstations, a preparation area for oral solutions and suspensions, and a staging area for medications awaiting

delivery to nursing units. There are automated processes for filling, packaging, and labeling of medications for a safer and more efficient workflow.

The IVAU is the largest part of the new pharmacy at more than 5,000 square feet. Dr. Farinre demonstrated the unidirectional flow of people and materials through the facility. There are separate areas for the compounding of nonhazardous and hazardous products, but each has similar workflows moving from the setup room to the compounding rooms through delivery to patient care units.

The IVAU has significant updates to make it safer and more efficient, including:

- 12 compounding rooms (compared with 3 in the old pharmacy)
- 10 biological safety cabinets (compared with 3 in the old pharmacy)
- 38 pass-through chambers equipped with high-efficiency particulate air (HEPA) filters
- 100% automated workflow supported by Omnicell IVX with remote product verification

Discussion

Dr. Forese commended the renovations and was particularly impressed with the efficiency and safety measures. She asked about the pharmacy staff's involvement with the renovation plans. Dr. Farinre said that she was not involved in the original design, since she only joined the Clinical Center in 2019; however, once she joined, pharmacy leadership made recommendations to update the design to accommodate the needs of the staff. Dr. Gilman added that there have been two complete turnovers of pharmacy leadership since the FDA visit in 2015. Although Dr. Farinre's team made some changes to the original design, these were necessary and important for supporting the pharmacy staff.

Update: Clinical Center Facilities Projects

Dan Wheeland, P.E., Director, NIH Office of Research Facilities

Mr. Wheeland announced that the quarterly meeting with Congressional Appropriations Committee staff resulted in increases in funding. The buildings and facilities appropriation was increased from $200 million to $250 million, which is a 25% increase. This is the largest percentage increase of all NIH appropriations and now represents the base for future year appropriations. There was also an increase in Special Authority funding, which is also known as General Provision 216. The increase was from $3.5 million per project to $5 million per project. The aggregate amount for Special Authority funding increased from $40 million to $100 million. This funding increase will enable NIH ICs to use more of their funding for repairs and improvements.

These increases in funding are likely the consequence of the National Academies of Sciences, Engineering, and Medicine consensus study about the backlog of maintenance and repair. Also, the President's FY 2023 budget proposes an increase in buildings and facilities funding from $250 million to $300 million, so hopefully this proposed budget is enacted.

Projects Recently Awarded: C103157 Surgery, Radiology, and Laboratory Medicine (SRLM) Building, Including Catheterization Lab and Interventional Radiology

Mr. Wheeland showed a rendering of the new SRLM building. The design-build team will be led by Hensel Phelps. ZGF was the architect of record for the Mark O. Hatfield Clinical Research Center and is familiar with the existing building. RMF, which is doing the mechanical and plumbing engineering, has worked with NIH before. The award amount for this project is $638 million.

Mr. Wheeland thanked the Board for their support for this project. The CCRHB wrote an important letter that helped secure the support for the SRLM building.

Projects That Have Achieved Substantial Completion of Construction

Mr. Wheeland reviewed projects that are were recently completed:

- A combination positron emission tomography–magnetic resonance scanner that promotes simultaneous imaging was recently completed and will benefit the patients and the staff.
- A quarter-mile of piping in the Clinical Center was recently replaced. The previous piping was oversized, which made the water velocity slower and led to creation of sediment and biofilm. Also, the old piping was made of galvanized pipe, which had some corrosion. The new piping is smaller and made of copper. Mr. Wheeland recognized the exceptional planning and patience of the Clinical Center staff, who had to deal with a 20-hour water outage for the pipes to be replaced.
- A sterility laboratory for the Department of Laboratory Medicine was completed. This new facility dramatically enhances the Clinical Center's ability to ensure items are properly sterilized.
- A cell processing facility for the Center for Cellular Engineering was recently completed. The commissioning, qualification, and validation will be completed in April 2022, and the environmental monitoring and performance qualification is scheduled for June 2022.

Projects Under Construction

Mr. Wheeland highlighted projects that are currently underway:

- Improvements are being made to the sterile processing areas in B1 and level 2 to improve safety, production, and workflow regulatory compliance. These steps will also be implemented in the new SRLM Building.
- The E Wing of the Clinical Center is still being renovated. These updates will improve the capabilities of the Department of Transfusion Medicine, including cell processing and blood banking. This project should be completed in May 2023.
- Black Start generators will be installed to generate steam and chilled water for the Clinical Center. Given the impacts of climate change, the team is aware of the need to develop a resilient infrastructure for this project, which should be completed by June 2023.
- There are plans to build a new utility vault for all electrical equipment that serves the entire Building 10 complex.

- The current underground patient parking garage at the Clinical Center has deteriorating concrete and poses a security risk due to the need to inspect all vehicles. This parking garage will be closed, and a new patient parking garage will be built.
- The additional protective isolation patient care unit in the pediatrics inpatient ward is halfway done. This ward currently has 16 standard patient rooms, 4 protective equipment rooms, and 4 airborne infection isolation rooms. This project involves converting four patient rooms into protective equipment rooms with HEPA filtration and positive pressurization. One airborne infection isolation room will turn into a dual-purpose room by adding HEPA filtration.

Discussion

Dr. Forese said that the CCRHB was able to tour the Clinical Center a few years ago and hopes that members would be able to tour the facilities again soon.

Dr. Shannon commented that the facilities projects have made extraordinary progress. He added that the new SRLM and renovations to the pediatric inpatient ward reflect the direction of the Clinical Center's research portfolio, which is focused on cell-based therapies and genetics.

Many Board members shared their praise of these facilities projects in the chat.

Identification of the *VHL* Clear Cell Kidney Cancer Gene: Molecular Diagnosis, Precision Surgery, Oxygen Sensing, Precision Therapy

W. Marston Linehan, M.D., Chief of Urologic Surgery and the Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute

Dr. Linehan said that in the 1980s, kidney cancer was thought to be a single disease and was treated with the same surgery and the same drug treatments. But there is a growing understanding that kidney cancer is composed of many different diseases. Each has a different histology, shows different disease courses, responds differently to treatments, and is caused by different genes. For example, 18 genes that cause kidney cancer have been identified, and there are 14 genetically defined types of hereditary kidney cancer.

Most of what is known about the genetic basis of kidney cancer is based on data from studies of families. At the Clinical Center, more than 3,000 patients from 1,500 families are being studied to understand more about various types of kidney cancer, including clear cell, papillary, chromophobe, and oncocytic renal cell carcinomas.

Over the past 38 years, research at the Clinical Center has led to definition of eight novel kidney cancers and identification of nine disease genes. This research would not have been possible anywhere else but the Clinical Center. Dr. Linehan's research team published a paper in *Nature* that showed consistent loss of chromosome 3 in tumors from patients with sporadic clear cell kidney cancer. This work was published 17 years before the human genome was sequenced, so the team decided to study hereditary kidney cancer genes to discover the genes for non-hereditary, sporadic kidney cancer. The goal of this research was to find precision approaches for diagnosis, surgery, and therapy.

Patients affected with von Hippel-Lindau (VHL) syndrome, the first hereditary kidney cancer syndrome that Linehan and his colleagues studied, are at risk for the development of tumors in several organs, including the kidneys. VHL syndrome increases the risk for early onset, bilateral, multifocal clear cell kidney cancer, which can lead to kidney tumors that can spread and metastasize. Over the course of this research at the Clinical Center, 53 VHL patients developed metastatic cancer, and more than 800 kidney surgeries to treat VHL kidney cancer patients have been done. VHL patients are also at risk for pancreatic neuroendocrine tumors, VHL syndrome–associated cerebellar and spinal hemangioblastomas, and retinal angiomas.

The current approach at the Clinical Center is to use precision clinical management for each type of genetically defined kidney cancer. For VHL syndrome, the team uses an active surveillance approach to monitor the tumors instead of immediately removing the entire kidney. Once the largest tumor reaches 3 centimeters in size, a robot-assisted partial nephrectomy is performed by enucleating and removing the tumors. Since adopting this approach for managing VHL syndrome, no patients have developed metastatic disease.

To better understand the genetic basis of VHL syndrome, Dr. Linehan and his colleagues studied families with VHL syndrome and traced the *VHL* gene to the short arm of chromosome 3, the same region identified as the genetic basis for sporadic clear cell kidney cancer. Using genetic linkage analysis and physical mapping, the team was able to identify the *VHL* gene in 1993, nearly 10 years after starting the project. This was one of the earliest human cancer genes identified and led to a blood test that helps identify *VHL* carriers.

Next, Dr. Linehan's team tested tumors from patients with sporadic, nonfamilial clear cell kidney cancer. They found either the *VHL* mutation or methylation silencing of the *VHL* gene in 91% of the tumors tested. The *VHL* mutation was not found in other types of kidney cancer, indicating its role specifically in clear cell kidney cancer.

Once *VHL* was identified, the next steps were to understand the molecular mechanism of the disease. First, the group, along with William G. Kaelin, Jr., M.D., from the Dana–Farber Cancer Institute, found that the VHL protein forms a complex with the elongin B and elongin C proteins. Subsequent research found that *VHL* regulates genes that are oxygen-sensitive. In normoxia, VHL forms a degradation complex with elongin B, elongin C, and Cullin 2 that targets hypoxia-inducing factor (HIF) for degradation. During hypoxia, the VHL complex cannot mark HIF for degradation and HIF accumulates, which can lead to cancer.

In 2019, the Nobel Prize in Physiology or Medicine was awarded to Dr. Kaelin, Sir Peter J. Ratcliffe, M.D., and Gregg L. Semenza, M.D., Ph.D., for their work on how cells sense and adapt to oxygen availability. The Nobel Prize assembly cited research conducted at the Clinical Center as being vital for this discovery.

This research was the foundation for the development of therapeutic agents that targeted the VHL/HIF pathway. Subsequent research found that HIF2 was critical for kidney cancer tumorigenesis, and belzutifan, an agent which targets HIF2, was identified by scientists in Texas. The Clinical Center led the multicenter clinical trial to test belzutifan in *VHL* patients. In this trial, there was a 98% partial or stable response to treatment, in which 92% of target lesions in the kidneys decreased in size. For patients with cerebellar and spinal hemangioblastomas, 6% showed a complete response and 86% showed a stable or partial response to treatment. For

patients with pancreatic neuroendocrine tumors, 91% had an objective response rate, with 14% showing a complete response to treatment. The most impressive result was that belzutifan led to improvement or stable disease in 100% of *VHL* patients with retinal angiomas. Importantly, 2.5 years before these *VHL* patients were started on this trial, there were 53 surgical procedures to deal with tumors. In the 2.5 years after the trial, only three surgical procedures have been performed.

Dr. Linehan thanked the many researchers who have been involved in this work and the brave patients who participated in the trials.

Discussion

Ms. Berty congratulated Dr. Linehan on this wonderful research and thanked him for making the story easy to understand. Dr. Forese agreed that the story was relatable and action-packed.

Dr. Shannon said that renal cell cancers have a higher incidence among Black men and suggested that response rates to treatment could be analyzed based on a person's race or ethnicity. Dr. Linehan agreed that this type of analysis would be important. Both Black men and women have higher incidence of kidney cancer, but they are more often affected by papillary versus clear cell kidney cancer than are non-Black patients. The group wants to expand their efforts and understand racial and ethnic differences in kidney cancer and treatment response.

Dr. Gallin said that this story is an example of how partnerships between the basic science and clinical science communities leads to monumental discoveries and achievements, including a Nobel Prize. NIH and the Clinical Center are key factors in this accomplishment.

Ms. Royster shared her personal story of dealing with kidney disease and said that attentive doctors and novel therapies have helped her feel better. She was excited by this important work to help improve the lives of people with kidney cancer.

Adjournment

Dr. Forese thanked the presenters, NIH Clinical Center staff, and Board members. The next Board meeting is scheduled for July 15, 2022, and will be a hybrid meeting of in person and virtual.

Dr. Forese adjourned the meeting at 12:42 p.m.

Laura Forese

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Laura Forese, M.D., M.P.H.

Chair, NIH Clinical Center Research Hospital Board

Executive Vice President and Chief Operating Officer, NewYork–Presbyterian Hospital

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

Executive Director, NIH Clinical Center Research Hospital Board

Acting Director, NIH

Abbreviations and Acronyms

ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines
ADC	average daily census
ARPA-H	Advanced Research Projects Agency for Health
CAUTI	catheter-associated urinary tract infection
CCRHB	Clinical Center Research Hospital Board
CDC	Centers for Disease Control and Prevention
CEO	chief executive officer
CLABSI	central-line–associated bloodstream infection
COVID-19	coronavirus disease 2019
DART	days away, restricted, or transferred
DEIA	diversity, equity, inclusion, and accessibility
EUA	Emergency Use Authorization
FDA	U.S. Food and Drug Administration
FNIH	Foundation for the National Institutes of Health
FY	fiscal year
HBCU	Historically Black Colleges and Universities
HHS	Department of Health and Human Services
HIF	hypoxia inducing factor
ICs	Institutes and Centers

ICU	intensive care unit
IVAU	intravenous admixture unit
MOU	memorandum of understanding
NCATS	National Center for Advancing Translational Sciences
NDNQI	National Database of Nursing Quality Indicators
NHLBI	National Heart, Lung, and Blood Institute
NHSN	National Healthcare Safety Network
NIAID	National Institute of Allergy and Infectious Diseases
NINDS	National Institute of Neurological Disorders and Stroke
NIH	National Institutes of Health
OCMR	Office of Communications, Media Relations, and Patient Recruitment
OSTP	Office of Science and Technology Policy
P4	Permanent Pharmacy Placement Project
PASC	post-acute sequelae of COVID-19
RECOVER	Researching COVID to Enhance Recovery
RT-PCR	reverse transcription polymerase chain reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SRLM	Surgery, Radiology, and Laboratory Medicine Building
VHL	Von Hippel-Lindau