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Research News Quarterly

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Letter from the Editor

Our Research News Feature this month is an interview with Dr. Renee Wegryzn, who on October 11, 2022, was appointed first director of a new NIH agency named the Advanced Research Projects Agency for Health (ARPA-H).

Dr. Mallar Bhattacharya has described ARPA-H as follows: recent progress in medical research, from mRNA vaccines to cancer immunotherapy to advances in health systems research, has highlighted the power of rapid discovery coupled with implementation to transform healthcare. Recognizing the importance of supporting research aimed at solving major health problems, President Biden proposed this new agency in April 2021. Congress passed legislation in March 2022, authorizing ARPA-H within the Department of Health and Human Services. A budget of $1 billion was allocated for FY22 and $1.5 billion for FY23. ARPA-H will fund high-risk, high-reward research programs aimed at solving major health challenges, ranging from the molecular to social determinants of health. In President's Biden's words, delivered during an address in 2022, "ARPA-H will pursue ideas that break the mold on how we normally support fundamental research and commercial products in this country…Ideas so audacious that people say they just might work only if, only if, we could try. Well, we're about to try in a big way." ARPA-H has already issued a call for applications for Program Manager positions and for research funding. For our interview with Dr. Wegrzyn, we tried to design questions that would provide as much information as possible about ARPA-H and hope you enjoy reading it.

In this issue, we also have included a second interview, this time with Dr. Prescott Woodruff, Principal Investigator of SPIROMICS, a very large NIH- and COPD Foundation-funded nationwide study whose major goal is to advance understanding of patient heterogeneity in COPD. In a fairly concise interview, Dr. Woodruff provides a very insightful summary of the principal goals and findings of the two major studies within SPIROMICS.

In a third article, Karen Ridge, Erin Marie Nebel, Miriam Ridge, and Kamran Atabai MD have provided a wonderful description of the American Thoracic Society's Research Program. They provide information about its history, sources of income, processes for review, and amounts of awards. They also highlight 3 prior recipients of these awards and some of the ways in which the awards have helped them develop into successful and productive investigators.

In the subsequent article, Dr. Jen Alexander-Brett and Dr. Siddhartha Kapnadak have provided a detailed update on needs and opportunities in research related to lung transplantation. Amy Skiba, Executive Director of the Lung Transplant Foundation, also describes some of the ways in which investigators, working in this important area, can engage with patients and patient advocacy groups to facilitate a better understanding of the importance of the research and its likely benefits.

Also in this issue, Valerie Adelson, Associate Director, Government Relations, for the ATS updates us on some key leadership transitions.

Sincerely,

James K. Brown MD
Chair, Research Advocacy Committee

Research News Feature

Interview with **Dr. Renee Wegrzyn**

Director, Advanced Research Projects Agency For Health (ARPA-H)

Thank you very much, Dr. Wegrzyn, for allowing us to interview you. You have an extremely impressive record as a leader in moving science and biotechnology forward, especially through positions you have had in the federal government. In the relatively recent past, however, you took a job in private industry. What factors led you to return to working in the federal government and to accept the position as ARPA-H Director?

Thank you for the opportunity to talk with you about the Advanced Research Projects Agency for Health (ARPA-H). Serving Americans as the first ARPA-H director is the opportunity of a lifetime to improve health outcomes for all Americans. Throughout my career, whether focused on gene therapy or biosecurity, my motivation has always been "how do we create health solutions that can be implemented in the real world?" That's what ARPA-H aims to do.

The American Thoracic Society (ATS) is a world leader in accelerating the advancement of respiratory health with over 16,000 clinicians, scientists, and patient advocates in its membership. How can our Society best assist ARPA-H to achieve its goals?

It's essential to remember that our end goals and those of ATS are aligned – we all want to get better health solutions to people faster. To do what I envision for ARPA-H requires collaboration with a very broad group of stakeholders, both federal and nongovernmental, from patients to caregivers to industry, to ensure that we're taking on the right problems and delivering solutions that work in the real world for the American people. Success for us means transitioning those solutions so they can reach everywhere and ensure better health for everyone.

President Biden, in his original announcement about the creation of ARPA-H, stated that curing cancer, diabetes mellitus, and Alzheimer's disease would be three of its major goals. The current ARPA-H website suggests that ARPA-H may focus more on developing or improving devices, sensors, complex systems, platforms, and technologies. What reassurances can you provide that future focus areas of ARPA-H's research projects will benefit ATS members? Also, how do you envision ARPA-H projects directly engaging with patients?

President Biden's vision for ARPA-H – borrowing from his own words – is an organization that will pursue audacious ideas that break the mold on how we normally support fundamental research and commercial products in this country. ARPA-H has an enormous opportunity and responsibility to find and accelerate health advances to achieve better, equitable outcomes for all people.

One of the most exciting aspects of ARPA-H is that we are not going into research with a predetermined focus on one particular cure or treatment. One of the very best ways ATS members can get involved is to apply to be a Program Manager. We will empower Program Managers to pursue solutions that they know from their direct experience can improve health for everyone and with robust evidence that these solutions are possible. By hiring a diverse set of Program Managers, we hope our solutions will one day benefit your members. Regarding patient engagement, we have been meeting with, and will continue to meet with, diverse stakeholders to understand patient challenges. These include the patients themselves.

As a stated goal of ARPA-H is to support transformative research to effect biomedical and health breakthroughs, what role will fundamental, discovery science focused on biological mechanisms have in projects funded by ARPA-H? Must core technologies already be developed in order to be considered for support by ARPA-H?

Not at all. In fact, ARPA-H welcomes applications for Program Managers who come with an idea – and the expertise to execute it– that has the potential to be the next transformative health solution. As well, the programs that result will seek support from a wide variety of performers through Broad Agency Agreements. We have a huge opportunity open right now to provide support for transformative ideas via an agency-wide Open BAA. I encourage all people interested, and with great ideas to improve health, to explore these many ARPA-H opportunities.

Can you specify the unique attributes of a competitive ARPA-H project/program proposal that would distinguish it from a competitive NIH project/program proposal?

Funds will be allocated to Program Managers that have successfully defined problems that cannot be solved through traditional methods. Those Program Managers will create programs through which several teams, with unique approaches to solutions, will be funded. Funding typically will come from contracts and not grants. Program Managers will justify their budgets, and actively manage their programs, with frequent checkpoints to ensure we're funding success.

How will applications received via the current Broad Agency Announcement be assigned to Program Managers? Will Program Managers work with funded groups within a certain portfolio or disease area, modifying or expanding proposals to create a thematic unity?

To receive funding, programs must align with ARPA-H's mission to accelerate better health outcomes for everyone and must undertake research that cannot be addressed with existing federal funding ecosystems, components, or commercial markets. Efforts will fall into one of four focus areas:

- Health Sciences Futures (expanding what's technically possible): Accelerating advances across research areas and removing limitations that impede progress towards solutions. The tools and platforms developed apply to a broad range of diseases.
- Scalable Solutions (reaching everyone quickly): Addressing challenges that include geography, distribution, manufacturing, data and information, and economies of scale to create programs that result in impactful, timely, and equitable solutions.
- Proactive Health (keeping people from being patients): Reducing the likelihood that people become patients. Preventative programs will create new capabilities to detect and characterize disease risk and promote treatments and behaviors to anticipate threats to Americans' health, whether these are viral, bacterial, chemical, physical, or psychological.
- Resilient Systems (building integrated healthcare systems): Developing capabilities, business models, and integrations to weather crises such as pandemics, social disruption, climate change, and economic instability. Resilient systems sustain themselves between crises to better achieve outcomes and advance American health and wellbeing.

We hope that diversity, in every shape and form (gender, race, geographic location, and areas of scientific expertise), will be represented across ARPA-H Program Managers. One concern is that women and members of under-represented minority groups may not have the financial and job security that would permit them to apply for term-limited, 3-6 year Program Manager positions. Could you comment on this potential concern?

ARPA-H's success relies on the promotion of a culture that is administratively and scientifically nimble. It must have diversity, in all its forms, well-represented. We can't reach all Americans unless we work to reflect all Americans. Diverse viewpoints from inside and outside our agency will inform our decision-making.

We will pay Program Managers very competitively. When it's time to transition from the role, we will aim to support our Program Managers to ensure they have not only a soft landing but also have learned from their ARPA-H experiences such that they are ready to lead elsewhere. That was my experience at the end of my DARPA term, and I'm grateful for it.

ARPA-H recently celebrated the first anniversary of its enactment. If you could project ahead to the end of the agency's second year, what goals for ARPA-H do you hope to have achieved by that time?

We're on track to have at least 15-20 Program Managers hired by the end of our second year. We will have our first programs launched much sooner than that. In addition, this year and beyond, ARPA-H will be supporting and leading efforts to encourage the generation of cutting-edge ideas from health and science communities including payers, providers, patients, and more.

Understanding and Addressing COPD Heterogeneity:

An Interview with SPIROMICS Principal Investigator Dr. Prescott Woodruff

By Mallar Bhattacharya, MD

COPD is the third leading cause of death worldwide, and treatments to reverse accelerated lung function decline in the disease are urgently needed. A major focus of the current science of COPD is to advance understanding of patient heterogeneity, with the goal of refining patient stratification and enhancing outcome measures for clinical trials aimed at precision therapies.

Sub**P**opulations and **I**nte**R**mediate **O**utcome **M**easures In **C**OPD **S**tudy (**SPIROMICS**) is an NIH-and COPD Foundation-funded, nationwide collaboratory focused on characterizing the clinical and molecular heterogeneity of patient populations with COPD. In the original study, known as SPIROMICS I, a national network of 12 centers enrolled a prospective cohort of 2,982 patients for

a 3-year prospective study, stratifying enrollees into four groups: non- smokers, smokers without airflow obstruction, mild/moderate COPD, and severe COPD. Patients were assessed at baseline and at annual follow up visits for clinical status, measurement of plasma analytes and lung function, computed tomography of the chest, and in some cases bronchoscopy. Since the beginning enrollment in 2011, the study has resulted in nearly 100 peer-reviewed articles based on insights from data collected by SPIROMICS investigators and advanced knowledge about sources of clinical, radiographic, and molecular heterogeneity in COPD.

The second phase of the study, SPIROMICS II, began in 2017 under the leadership of contact PI Dr. Prescott Woodruff, Chief of Pulmonary, Critical Care, Allergy, and Sleep Medicine at the University of California, San Francisco. Here we provide a transcript of our recent interview to learn about SPIROMICS II from Dr. Woodruff, who provides insight into the state of the art in COPD research:

Thanks for joining us and providing our readers your perspective on the cutting edge in clinical COPD research. On a personal note, how did you become interested in COPD?

COPD is a major cause of mortality and morbidity worldwide, and I've always been motivated to study diseases with major public health impact. In addition, when I started studying COPD, I felt it was not getting the attention it deserved. It may be because patients themselves were sometimes implicitly blamed for their condition, because of the role of smoking. COPD is a major worldwide health concern that we must attend to, and what's more, a significant proportion are never smokers.

How would you characterize the major findings of SPIROMICS I, and what in your view have been among the most impactful discoveries?

One of several impactful discoveries from SPIROMICS I was that almost half of smokers with preserved lung function had symptoms and activity limitation referable to lung disease. A corollary finding was that increased sputum mucin concentration was highly prevalent in patients with COPD but also in symptomatic smokers with preserved spirometry. We think this phenotype is due to mucus-related nonobstructive chronic airway disease.

Did these insights lead to the research priorities conceived for SPIROMICS II, and what are the major aims now?

In fact, the presence of symptoms and increases mucin concentration in smokers with preserved spirometry was the focus of Aim 1 of the SPIROMICS II funding proposal; our longitudinal studies of this population are the subject of our ongoing work. Aim 2 was to study the longitudinal progression of emphysema and to understand whether its origins were in small airways disease or occult vascular diseases. Longer follow-up than was available in SPIROMICS 1 was required (7 as opposed to 3 years). Aim 3 will focus on heterogeneity in exacerbations, with the working hypothesis that differences in both triggers and host response will determine outcomes.

What has consortium-based, team science enabled that single centers might not have accomplished? What were some challenges?

Increased participants is obviously one important advantage, but in addition, each center has unique, nonoverlapping scientific expertise. Therefore, we are able to undertake studies with multiple levels of analysis—including biology, radiology, clinical features, and physiology. Generically, network studies can pose a challenge if investigators across the many centers are not aligned and enthusiastic about working together. Thankfully, that was not an issue in SPIROMICS, and we have developed many fruitful collaborations across centers.

How does SPIROMICS II partner with industry to translate advances to the clinic?

From the beginning, we invited industry representatives to attend our presentations and scientific working groups to add their perspective on how research priorities could be aligned with drug development. This includes identifying clinical outcomes that are useful for clinical trials, stratification of patients according to tractable biological pathways, and developing approaches to using clinical technologies, such as radiology, for outcome assessment.

What do you see as the priorities for COPD research at present?

We have the working hypothesis that some aspects of COPD are more reversible than we currently appreciate. For example, if pathologic mucus plays a role in symptoms or airway obstruction through mucus plugging or promoting cough or sputum production, then those features could be targeted if we understood the biology of pathological mucus better. There may be other ways, such as treatment of microbiological colonization or other less appreciated contributors to symptoms or quality of life in COPD, through which we can improve the lives of patients with COPD. The focus is on low hanging fruit where we can make progress in the next 5 years.

The ATS Research Program: Moving the Field of Respiratory Medicine Forward

By Karen Ridge, Erin Marie Nebel, Miriam Rodriquez, and Kamran Atabai MD

The American Thoracic Society (ATS) Research Program was established in 2004 to provide funding opportunities for early-career researchers in pulmonary, critical care, and sleep medicine to better support their research, education, and training (1). Since 2004, the Research Program has awarded $22.8 million in research grants to 334 investigators who have gone on to secure more than $784.8 million in federal funding. That is a return on investment of $34 per dollar awarded.

The Research Program was established to fund science of the highest caliber, foster the development and training of future leaders in research, and develop strong collaborations between ATS and other non-profit organizations and the health care industry with shared interest in supporting research. The program encourages promising early career investigators to devote their talents to research and aims to prevent losing young scientists because adequate funding is not available to support research. The program provides "seed funding" that allows researchers to generate the preliminary data necessary to successfully compete for larger grants for the next stage in their research careers.

The ATS maintained its commitment to research in 2020 despite having to cancel the ATS International conference and the ATS Research Program Benefit, the largest fundraising activity in support of the program, due to the COVID-19 pandemic. During the 2021-2022 grant cycle, the ATS Research Program supported thirteen early-career investigators with $865 thousand dollars in funding. Since the pandemic, the ATS Board of Directors has made supporting the ATS Research Program a priority. Nine research awards were made in the latest round, including the ATS Diversity Grant, ALA/ATS/CHEST Foundation Respiratory Health Equity Research Award, and the ATS/CSL Behring Research Award in Acute Respiratory Distress Syndrome.

We believe that it is of the utmost importance to continue supporting the next generation of researchers with an eye towards delivering the scientific insights and progress our patients count on and deserve. The ATS Research Program is funded through generous individual donations from the ATS membership, our non-profit and pharmaceutical partners, and the annual ATS operating budget. You can support the ATS Research Program and ensure its longevity by making a donation and/or attending the ATS research dinner.

Each summer a Call for Proposals is issued for research projects in all aspects of pulmonary, critical care and sleep medicine. The Scientific Grant Review Committee, currently chaired by Kamran Atabai, MD and Erick Forno, MD, MPH, ATSF, review all proposals using an NIH style grant review process to determine that cycle's recipients. The winners are recognized by the ATS president at the International Conference Opening Ceremony.

ATS grants have had a significant impact on science – and on scientific careers. Here we profile three past awardees who exemplify the spirit of the ATS Research Program: Megan Ballinger, PhD; Deborah Winter, PhD; and Bria Coates, MD.

Megan N. Ballinger, PhD (Figure 1), Assistant Professor of Internal Medicine, Division of Pulmonary, Critical Care and Sleep Medicine at The Ohio State University College of Medicine, was awarded the ATS Foundation/Genentech Research Grant in IPF in 2016 for her research on macrophage activation during pulmonary fibrosis. That same year, she also received the ATS Jo Rae Wright Award for Outstanding Science.

In 2019 Ballinger secured an R01 grant from NIH to investigate the role of macrophages in regulating pulmonary fibrosis. Her current research focuses on monocyte-to-macrophage differentiation in response to allergic inflammation or acute lung injury, as well as the role of monocytes and macrophages in pulmonary fibrosis.

"The ATS Research Program was vital to my career because it allowed me to transition from a research track position to a tenure track position," Ballinger said. "At my institution research track faculty members are unable to participate in graduate training or sit on various committees at the graduate school. The ability to secure a tenure track position enabled me to recruit and begin training graduate students when my R01 was funded."

Ballinger is now a dedicated leader in training new senior investigators. For example, she served on the leadership team of the Fellow to Faculty Boot Camp at the ATS 2019 International Conference. She has served on the ATS Members in Training and Transition Committee, the Nominating Committee, and the Planning and Evaluation Committee. She currently serves on the Publication Policy Committee.

Deborah R. Winter, PhD (Figure 2), Assistant Professor of Medicine, Division of Rheumatology at Northwestern University Feinberg School of Medicine, was awarded the ATS Foundation/Mallinckrodt Pharmaceuticals Inc. Research Fellowship in Sarcoidosis in 2017 and the ATS/Mallinckrodt Research Grant in Sarcoidosis in 2020 for her research on macrophages in sarcoidosis.

Winter is a computational immunologist mapping the gene regulatory networks of immune cells, with special focus on macrophages in rheumatic disease. She received awards as a Scholar for Arthritis Research from the Arthritis National Research Foundation (ANRF) in 2018 and a Sontag Fellow of the ANRF from The Sontag Foundation in 2020. In 2021 she secured an R01 grant from NIH to investigate transcriptional regulators in aging macrophages.

"As a computational immunologist with training in basic gene regulation, it has been a challenge to get a foothold for translational research into human disease," said Winter. "The ATS Foundation awards have not only helped support my specific investigations into sarcoidosis but also provided me with a steppingstone into the field of pulmonary research. I look forward to expanding this initial work into a robust research program with a fresh perspective applying genomic approaches to rheumatic and pulmonary diseases, such as sarcoidosis."

Winter currently serves on the Editorial Board of Arthritis Research & Therapy. Activities such as co-leading an interdisciplinary research networking group in 2017-18 demonstrate her commitment to sharing ideas, expertise, and support across research specialties.

Bria M. Coates, MD (Figure 3), Assistant Professor of Pediatrics, Division of Critical Care at Northwestern University Feinberg School of Medicine, was awarded an ATS Foundation/American Lung Association grant in 2015 for her research on juvenile influenza, and an ATS Unrestricted Grant in 2020 for her research on age-related COVID-19 susceptibility.

Coates investigates mechanisms underlying the differences between children and adults in the innate immune response to viral respiratory infection. Since receiving her 2015 ATS grant, she has been awarded both a K12 and a K08 grant from NIH. She received a K award grant from the Central Society for Clinical and Translational Research in 2020 and was recognized as a Crown Family Research Scholar in Developmental Biology at the Stanley Manne Children's Research Institute of Ann & Robert H. Lurie Children's Hospital of Chicago in 2021.

Said Coates, "Support from the ATS was instrumental to my development as an early physician-scientist. Without the support of my ATS grant and constructive feedback from the reviewers, I would not have been able to obtain the preliminary data necessary to successfully compete for my K awards from the NIH."

Coates now serves on the ATS Research Advocacy Committee and on the Editorial Board of *American Journal of Respiratory Cell and Molecular Biology*. She has become a leader in training the next generation of early-career researchers, heading a research team of mentees who have won their own awards.

As demonstrated by these awardees, the ATS Research Program supports respiratory researchers at pivotal career points. This support enables focused, high-quality research and facilitates successful transition to more senior roles. Investigators can then, in turn, serve as mentors to new cohorts of early-career researchers. In short, the ATS Research Program ensures continued progress in pulmonary, critical care, and sleep medicine.

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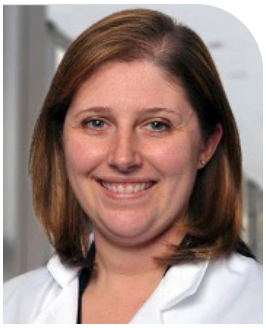

Figure 1. **Megan Ballinger, PhD**, 2016 recipient of the ATS Foundation/Genentech Research Grant in IPF.

Image credit: The Ohio State University College of Medicine

https://medicine.osu.edu/find-faculty/clinical/internal-medicine/megan-ballinger-phd

Figure 2. **Deborah Winter, PhD**, 2017 recipient of the ATS Foundation/Mallinckrodt Pharmaceuticals Inc. Research Fellowship in Sarcoidosis and 2020 recipient of the ATS/Mallinckrodt Research Grant in Sarcoidosis.

Image credit: Northwestern University Feinberg School of Medicine

https://www.feinberg.northwestern.edu/faculty-profiles/az/profile.html?xid=35765

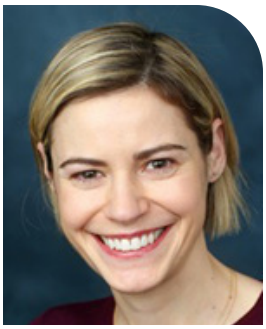

Figure 3. **Bria Coates, MD**, 2015 recipient of an ATS Foundation/American Lung Association grant and 2020 recipient of an ATS Unrestricted Grant.

Image credit: Ann & Robert H. Lurie Children's Hospital of Chicago

https://www.luriechildrens.org/en/doctors/coates-bria-m-3108/

Updates in Lung Transplantation and Research Opportunities

By Jen Alexander-Brett MD PhD, Siddhartha Kapnadak MD, and Amy Skiba*

*Ms. Skiba is Executive Director of the Lung Transplant Foundation

The practice of lung transplantation is evolving with recent developments including the emergence of new molecular diagnostics for acute rejection, changes in the definition and management of chronic rejection, and the very recent adoption of the Composite Allocation Score for prioritizing transplant candidates. Continued engagement of transplant patients in research will be critical to evaluating the benefit, cost-effectiveness, and equity of ongoing changes in clinical practice. Furthermore, as long-term lung transplant survival continues to lag other organs, advances in early detection and treatment of chronic rejection remain substantial unmet needs for improving patient outcomes.

While lung transplantation is an important treatment option for advanced lung disease, the number of patients in need far exceeds available donors. Donor allocation has evolved to support the overarching goals of improving transplant access for those most in need, avoiding futile transplants, and reducing the impact of geography. The U.S. lung allocation score (LAS) was implemented in 2005, prioritizing candidates based on projected 1-year waiting list mortality and likelihood of 1-year post-transplant survival, with the former weighted double. The LAS reduced waiting list mortality without impacting one-year post-transplant survival despite average recipients being older and sicker in the post-LAS era. Despite its benefits, the LAS did not address the impact of geography on allocation, historically prioritizing organs by Donor Service Area (DSA)'s, which were heterogenous in size, population, and donor availability, resulting in geographical disparities in waiting list outcomes. In 2017 the primary allocation unit was changed to a 250-nautical mile radius surrounding the donor hospital. However, several new concerns became apparent including potential to reduce efficiency (e.g., travel distances, costs), and the arbitrary nature of the 250-mile primary allocation zone by which sicker but slightly more distant candidates may be ineligible for organs. Moreover, several studies demonstrated that candidates who are allo-sensitized (with pre-transplant anti-human leukocyte antigen antibodies), of shorter stature, and blood group O have reduced donor access impacting waiting list survival.

To address these issues, a new lung Composite Allocation Score (CAS) took effect on March 9, 2023, prioritizing candidates based on:

1. Pre-transplant medical urgency
2. Projected post-transplant survival
3. Biological disadvantages (blood type, sensitization, height)
4. "Patient access" issues (points awarded for previous organ donors and age < 18)
5. Efficiency of donor organ transport to a given (nationwide) recipient.

In addition to removal of rigid geographic boundaries, the CAS utilizes five (rather than one)-year post-transplant survival and pre/post-transplant survival are weighted 1:1. These are important distinctions that prioritize longer-term outcomes after transplant. The CAS is projected to reduce waiting list mortality particularly among sicker candidates, with no change in 2-year post-transplant survival.

The "continuous distribution" framework is the first in organ transplantation and this novel approach brings numerous research opportunities to the lung transplant community, as described here.

First, a likely shift in demographics will require further understanding on multiple fronts, with the CAS projected to increase transplant rates in sicker and younger candidates, while reducing the proportion of transplants for chronic obstructive pulmonary disease and increasing waiting time for less urgent candidates. While transplant rates are projected to increase in candidates with blood group O and shorter stature, it is unclear if/how the changes may impact populations with reduced healthcare access including those with non-white race or socioeconomic barriers.

Second, the overall median distance from donor to recipient is projected to increase particularly for the sickest recipients. It will be important to understand the impact on ischemia times and risk of primary graft dysfunction, as well as optimal organ management strategies in the current era marked by increasing use of ex-vivo lung perfusion and other preservation systems. Costs, resource utilization, and optimal donor selection practices in the CAS era will also need further elucidation. Finally, although projections do not show decreases in transplant rates among lower volume transplant centers, it is unclear how center volume will interact with potential changes in transplant demographics and donor acceptance practices in the coming years. It's also unclear how these factors may impact practices and transplant outcomes.

Following lung transplantation, serial surveillance biopsies are typically obtained within the first year and represent the gold standard method for detecting acute rejection. Bronchoscopy with biopsy is not without risk, and recently developed molecular diagnostic tests including donor-derived cell-free DNA (cfDNA) or gene expression

profiling (GEP) assays performed on peripheral blood are a welcome supplemental diagnostic tool for allograft injury. Cell-free DNA assays are based upon detection of the small quantity of circulating donor-derived extracellular (cell-free) DNA released from the allograft in the setting of cellular damage. Blood samples are subject to highly sensitive next-generation sequencing to yield the fraction of cell-free DNA derived from the allograft. Based on analysis of patient cohorts in multiple solid organ transplant populations, threshold percentages of donor-derived cfDNA have been validated as a measure of allograft injury that correlates with acute rejection on tissue biopsy. The demonstrated utility of these supplemental methods for surveillance in patients at increased risk for biopsy have prompted recent Medicare coverage of testing and subsequent widespread uptake among transplant programs across the country. However, additional research is needed to guide interpretation of these less invasive methods when other forms of lung injury are present, particularly in the presence of infection, antibody mediated rejection and early chronic rejection. Furthermore, these tests are based on expensive and specialized methods. Therefore, technological advancements, as well as cost-benefit analyses, will be needed to support insurance coverage. Most importantly, analysis of the impact on overall rates of chronic rejection and survival post-lung transplant will better define the role of molecular diagnostics in transplant program surveillance protocols going forward.

Chronic rejection stubbornly remains the greatest barrier to long-term survival post lung transplant, with a current median survival rate of 6.0 years. Historically, the clinical diagnosis bronchiolitis obliterans syndrome (BOS), with obstructive physiology and the obliterative bronchiolitis pathological correlate, were considered the hallmarks of chronic rejection. While that pattern remains dominant, other forms of chronic rejection are now recognized. An example is restrictive allograft syndrome (RAS), which is characterized by restrictive physiology, radiographic infiltrates and histopathology with features of alveolar damage and parenchymal fibroelastosis. Collectively, these entities along with mixed or undefined forms of chronic injury are now included under the umbrella term chronic lung allograft dysfunction (CLAD). The definition of CLAD is made regardless of subtype and based on a persistent (≥ 3 months) decline in FEV1 of ≥ 20%, with 4 stages encompassing a range of FEV1 from 80% to less than 35%.

There remain limited options for management of CLAD, with typical practice including addition of macrolide antibiotics, extracorporeal photopheresis (ECP), or otherwise intensifying immunosuppression. A multicenter Medicare sponsored clinical trial investigating the efficacy of ECP in lung transplant patients with CLAD has completed enrollment and programs are currently awaiting the results and subsequent decisions regarding future patient access. There have also been limited studies investigating the addition of antifibrotics or mesenchymal stem cell-based therapies in treatment of CLAD.

Research focused on interventions for CLAD going forward will likely need to consider heterogeneity of the process and anticipate potential differences in response within BOS and RAS subtypes. Currently, they are distinguished based on a combination of physiological impairment, radiographic features and the exclusion of other contributing processes. Future research protocols would benefit greatly from the availability of molecular diagnostics specific to CLAD, particularly if diagnosis could be made prior to onset of physiological impairment and with the ability to distinguish between the major subtypes BOS and RAS.

Given the numerous research questions to be addressed in lung transplantation, as a research community, how can we best partner with our patients to achieve the necessary advances in access, diagnostic capabilities, and outcomes? The Lung Transplant Foundation strives to help connect patients with researchers through dissemination of information about ongoing clinical trials and tissue specimen biorepositories to support basic-translational research into conditions for which these patients are referred for lung transplantation. These efforts continue to be especially critical for rare diseases, where the genetic basis is unknown and animal models are lacking. With respect to patient participation in clinical trials, many find the protocols or interventions difficult to understand, and it can be challenging to access more information. Likewise, patient education regarding chronic rejection is highly variable and improved understanding of the diagnosis and treatment options could facilitate better participation. Accordingly, the Lung Transplant Foundation is working on a one-page report for clinical trials that may be shared with patients and clinicians to facilitate recruitment into trials for CLAD. The Foundation also recently participated in an FDA Patient-Focused Drug Development meeting on the topic of BOS, which was summarized in a Voice of the Patient Report for which the link is here: https://lungtransplantfoundation.org/bos-voice-of-the-patient/.

Together, clinicians and patients can be empowered to improve outcomes in lung transplantation. The practice changes and advancements described above, along with ongoing clinical trials in CLAD, as well as the development of precision diagnostics and advancement of basic research into the fundamental pathophysiology that drives chronic rejection, all hold promise for better future outcomes.

Important Leadership Transitions

By Valerie Adelson MHA BSN RN

Dr. Monica M. Bertagnolli is Nominee for NIH Director

On May 15, President Bident nominated Dr. Monica M. Bertagnolli as Director of the National Institutes of Health (NIH), ending a lengthy vacancy at the federal agency. Dr. Bertagnolli was appointed in October 2022 as director of the National Cancer Institute, the first woman to occupy the position.

Dr. Bertagnolli joined NCI from Harvard Medical School, where she served as the Richard E. Wilson Professor of Surgery in the field of surgical oncology at Brigham and Women's Hospital in Boston. She was also a member of the Gastrointestinal Cancer Treatment and Sarcoma Centers at Dana-Farber Cancer Institute in Boston.

If confirmed by the Senate, Dr. Bertagnolli would oversee the NIH, which has traditionally enjoyed bipartisan support in Congress with a budget that now exceeds $45 billion. In addition, she would be at the center of a political controversy regarding the origins of the coronavirus pandemic. House Republicans have prioritized investigating the NIH's funding of research projects, in search of evidence that some of its grants may have inadvertently triggered COVID's spread.

Dr. Bertagnolli would be the second woman to head the NIH. Dr. Bernadine Healy was director of the Research Institute at the Cleveland Clinic Foundation when President George H. W. Bush tapped her in 1991 to become director of the NIH, its first woman head.

Dr. Rochell Walensky will Step Down at CDC

On May 5, U.S. Department of Health and Human Services Secretary Xavier Becerra announced the resignation of Centers for Disease Control and Prevention Director Dr. Rochelle Walensky. Dr. Walensky plans to depart from the public health agency at the end of June. The Biden administration officially ended the Covid public health emergency on May 11.

Last summer, Dr. Walensky launched a reorganization of the CDC, acknowledging that its "performance did not reliably meet expectations" during the COVID pandemic. Dr. Walensky's critics, including many Republicans in Congress, see her as responsible for confusing public health messaging about COVID. Both the COVID and Monkey Pox crises, and how CDC handled them, at times raised questions about how well the CDC functions within the federal government.

Under current law, President Biden will be able to appoint a new CDC leader without a requirement for Senate confirmation.

Dr. Walensky was appointed in December 2020 by then-President-elect Biden. As the head of Massachusetts General Hospital's Infectious Disease Division and Professor of Medicine at Harvard Medical School, Dr. Walensky was widely respected in public health circles for her work, including decades of HIV research.

Dr. James K. Brown, Chair, Research Advocacy Committee, commented on Dr. Walensky's resignation. Dr. Brown noted that "From a background as a physician-scientist with little experience running large institutions, Dr. Walensky successfully guided the CDC through the pandemic and generally helped restore its reputation. The ATS thanks Dr. Walensky for her contributions and looks forward to working with her successor."