Kidney Precision Medicine Project: **Hope for the Future**

By Jonathan Himmelfarb

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The Kidney Precision Medicine Project (KPMP) is a transformative initiative funded by the National Institute of Diabetes and Digestive and Kidney Diseases. It is designed to tackle the major public health burdens resulting from acute kidney injury (AKI) and chronic kidney disease (CKD). The rationale for KPMP is straightforward: Despite the significant impact of AKI and CKD on patient outcomes, no proven safe and effective therapies exist for AKI, and only a few are available for CKD.

The landscape of treatment for these kidney disease syndromes has not changed substantially in many years, and we have a poor understanding of AKI and CKD heterogeneity between individuals. Thus, at present we are not close to the precision medicine goal of finding the right treatment at the right time for the right patient with CKD and AKI.

The KPMP is focused on finding new ways to treat AKI and CKD by safely and ethically obtaining and evaluating human kidney biopsy specimens from individuals who volunteer to participate. The kidney tissue will be analyzed in multiple ways, including intensive cutting-edge molecular analysis and the innovative use of digital histopathologic analysis coupled with machine-learning tools. This kidney tissue will be used to create a human kidney tissue atlas in health and disease as a publicly available resource for patients, caregivers, and researchers.

The KPMP focuses on people who have very common types of kidney disease for which we don't really know the best treatment. With this focus, we can have the most impact in improving the outcomes for people everywhere living with kidney diseases. If we are successful, the KPMP will allow the entire kidney community to discover critical cells, pathways, and targets for novel therapies and to eventually devise individualized treatments based on these new insights. This is the essence of what kidney precision medicine is all about: bringing the right treatments at the right dose at the right time to the right patient with kidney disease.

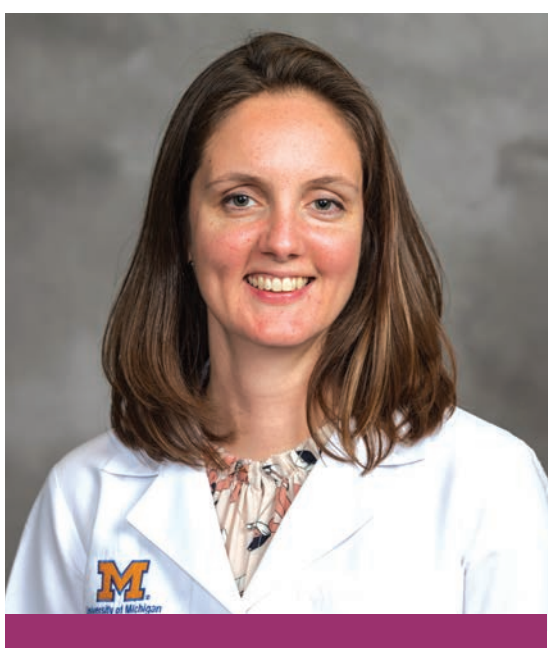
There are several unique and exciting components to KPMP. One of the most important aspects of this project is that we've put patients at the forefront of our study. Patients are involved in all aspects of the study as equitable partners in KPMP. For example, our Community Engagement Committee is primarily made up of kidney disease patients who have helped develop our approach to informed consent and have provided multiple recommendations during protocol development. In addition to broad patient involvement, KPMP has a large and diverse group of stakeholders, each dedicated to the long-term success of the project. Also, KPMP is committed to fostering the development of junior investigator careers, including providing funding and travel awards for early-career investigators to attend our face-to-face meetings. We hope that KPMP contributes to fostering the next generation by strengthening the pipeline of researchers, clinicians, and educators.

On a personal level, it is both humbling and inspiring to be able to serve as part of the leadership for this historic project. For my entire professional life, I've taken care of patients with varying stages and types of kidney disease and have wished for more and better treatment options. I am hopeful that at the end of the day, this project will help us fully understand our patients' medical conditions in ways that we often do not understand now, and completely change the way we care for our patients for the better.

Jonathan Himmelfarb, MD, is professor of medicine at the University of Washington, director of the Kidney Research Institute, and co-director of the Center for Dialysis Innovation. He is co-principal investigator for the Central Hub of the Kidney Precision Medicine Project.

Perspectives from a Junior Investigator in the Kidney Precision Medicine Project

By Laura H. Mariani



Laura H. Mariani

"The future belongs to those who believe in the beauty of their dreams."

— Eleanor Roosevelt

Working with the Kidney Precision Medicine Project (KPMP) consortium as a junior investigator is a tremendous opportunity for me, with tangible training experiences and many more intangible moments for professional growth and creativity.

Certainly, the tangible training experiences are exceptional, and the KPMP consortium has not only allowed, but encouraged, contributions from junior investigators, allowing us to learn best by doing. In particular, each research team from a recruitment site interpreted the request for application independently and proposed an approach relevant to their own institutions to recruit patients with either chronic kidney disease or acute kidney injury for a kidney biopsy to be used for research. But as the recruitment sites were assembled and became a single KPMP research team, the protocols were harmonized and transformed to a shared approach, accommodating differences in institutions and patient populations along with the needs of the tissue interrogation sites.

I learned the true value of multidisciplinary perspectives to accomplish this task and other tasks of a large consortium. The products are made infinitely better by the inclusion of perspectives from patients, clinicians, study coordinators, clinician and basic scientists, programmers, biostatisticians, ethicists, and, perhaps most important, project managers to keep everyone on task.

And then, to be able to participate in translating a protocol into the nuts-and-bolts tools necessary to launch a multisite study is the sort of invaluable training experience provided to KPMP junior investigators. There is no better way to really understand a study than to help write the manual of procedures, draft questions on case report forms, sit with a programmer building

the data collection system, or train a study coordinator. This process of iterative improvement, listening to unique perspectives, and creativity to address barriers and compromise applies to scientific tasks well beyond protocol development to study execution, data generation, interpretation, and communication.

These tangible training experiences occur simultaneously with the intangible experiences. Principally, the consortium expands the pool of mentors and collaborators just by the number and diversity of the KPMP scientific team.

KPMP supports a travel award program for trainees and junior faculty to attend the in-person investigators' meetings and bring their work to a poster session. As junior investigators, we often work on projects in very small groups at our home institutions. To be able to discuss not only individual projects but also ideas, hypotheses, data sources, and approaches with investigators beyond our home institutions is instrumental in expanding our scientific training and resources. This exchange happens at the poster sessions and also in the main meeting and during working group calls in between. To listen to scientists with different approaches and training share data and ideas, but also, and perhaps more valuably, critiques, limitations, and suggested alternatives truly broadens my tools and scientific knowledge. Not unlike pursuing clinical training in more than one institution wherein you learn that there are multiple ways to practice high-quality clinical medicine, KPMP fosters a community of mentors and trainees who teach one another the value and limitations of a much-expanded number of approaches.

The fundamental overarching benefit of being a junior investigator in KPMP is the pursuit of a beautiful dream: to leverage the explosion of high-dimensional data generation, tissue image analysis, machine learning, and bioinformatics analyses to answer fundamental questions about some of the most common kidney conditions: diabetic and hypertensive CKD and AKI. Not only do we describe these conditions and their presentations but we build a resource based on human tissue, which can be used by the entire nephrology community to transform our clinical practice and allow us to answer the most basic questions asked by our patients: 1) What disease do I have? 2) What will happen to me? And 3) What can you do about it?

The KPMP embraces this goal by committing to truly open science by building the kidney tissue atlas, which will make the data, so generously provided by participants, readily available and accessible to researchers outside of KPMP and also to patients and clinicians to tackle these fundamental questions.

When I read the personal statements of nephrology fellowship applicants, I am reminded of the enthusiasm that nephrology can inspire as applicants describe their satisfaction in grasping renal physiology, the devastation at watching kidney failure in their patients, and their awe of the importance of the healthy kidney to other organ systems. KPMP captures that enthusiasm by bringing together investigators who want to tackle big questions by working collaboratively and openly. That enthusiasm is infectious.

It is easy to believe in the big dream that the conversations I have with my patients now will be vastly different in the future as we discuss the best medication, out of many choices, to protect their kidneys from injury, speed recovery, and prevent progression to kidney failure. ■

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Policy Update

Trend of Falling Applications Resulting in Decrease of KUH Funding Must Be Reversed

By Ryan Murray

After a sustained effort in support of National Institutes of Health (NIH) funding by the American Society of Nephrology (ASN) and the broader kidney community, Congress passed a $2 billion funding increase for NIH for fiscal year (FY) 2019. Additionally, the National Institute of Diabetes and Digestive Kidney Diseases (NIDDK) received a 5% increase that was widely celebrated by the kidney community.

Unfortunately, the gains seen by NIH and NIDDK have not translated into funding for the Division of Kidney, Urologic, & Hematologic Diseases (KUH), which saw a 2% decrease in total funding. NIDDK is a payline-driven funding program that "follows the science," meaning that Divisions that receive more applications receive more funding and are, therefore, able to provide more awards. So, while NIDDK has continued to see its budget increase due to congressional appropriations, the allocations to KUH have lagged when compared to other NIDDK Divisions.

A central portion of the NIDDK portfolio are R01s, which contributed to 93% of the NIDDK increase in total awarded dollars from 2017 to 2018. Despite its significance to the overall NIDDK portfolio, KUH has seen a slow erosion of its R01s over the years and experienced an 8.7% decrease in R01 applications from 2018 to 2019. More troubling is that this trend will continue to grow unless there is a significant increase of early stage investigators (ESI) applying for funding; however, KUH saw ESI applications fall a staggering 27% in only one year—2018 to 2019.

Compounding the problem is the fact that the kidney community is losing the battle on two fronts. Not only are the total number of KUH applications stagnant compared to the rest of NIDDK, but the applications are historically awarded less funding. The average total cost of NIDDK competing R01 awards in 2018 was $484,019, while the average in KUH was $461,000. ASN leadership strongly encourages every investigator applying for funding to explicitly ask for what their study needs and to justify those numbers.

"Kidney patients are desperately waiting in our dialysis clinics, hospitals, and offices for new therapies. It is solely up to us now, as a community, to generate hope that reaches from patients and their families to potential future nephrologists by prioritizing existing and emerging programs that bolster cutting-edge investigative activities and attract the best minds to the nephrology specialty. ASN has initiated several programs with this goal in mind and will continue to identify new opportunities with the goal of stemming this tide," Crystal A. Gadegbeku, MD, FASN, ASN Policy and Advocacy Committee Chair, said in a recent statement.

ASN has launched several initiatives to foster interest in careers in nephrology and research and to advance the careers of those who have already entered the nephrology workforce including:

- **Kidney STARS** (Students and Residents) provides complementary membership to the society, $1000 in travel support, and complementary registration to attend the ASN Annual Meeting at Kidney Week, in Washington, DC, and tailored events and networking opportunities onsite.
- **Kidney TREKS (Tutored Research and Education for Kidney Scholars)** seeks to accomplish the same goal through a weeklong research course retreat and long-term mentorship program.
- **KidneyX**, a new public-private partnership between ASN and the U.S. Department of Health and Human Services (HHS), aims to accelerate breakthroughs to promising new technologies for people with kidney diseases and tangentially spur interest in nephrology by positioning it as an exciting and growing field.
- **ASN Foundation for Kidney Research Career Development Grants Program** provides funding for young faculty to foster evolution to an independent research career and a successful application for a National Institutes of Health (NIH) full R01 grant or equivalent. By the end of the grant period, a recipient will have an independent research career and be competitive for federal and nonfederal funding.

Similarly, NIDDK has several programs geared toward fostering the next generation of kidney investigators with the goal of ensuring they become an independent researcher:

- **NIH Summer Internship Program in Biomedical Research (SIP)** provides a developmental training experience to promising high school, undergraduate, and graduate students who have expressed a strong interest in or are studying disciplines related to biomedical sciences.
- **Postbaccalaureate Intramural Research Training** program provides recent college graduates who are planning to apply to graduate or professional school an opportunity to spend one or two years performing full-time research at the NIH.
- **Undergraduate Scholarship Program** offers competitive scholarships to students from disadvantaged backgrounds who are committed to careers in biomedical, behavioral, and social science health-related research. The program offers paid research training at the NIH during the summer and paid employment and training at the NIH after graduation.
- **Predoctoral to Postdoctoral Fellow Transition Award** seeks to recruit exceptional graduate students who are recognized by their institutions for their high potential and to incentivize them to pursue a Kidney, Urologic or Hematologic postdoctoral position.

ASN encourages its members to share both its and NIDDK's unique opportunities with potential researchers who are interested and eligible. The society will continue to advocate for increases to the NIH and NIDDK budgets. By being united and fighting this battle on multiple fronts, we can make certain that any budget increase NIDDK receives from congressional appropriations is reflected in a proportional increase to KUH. ASN will keep readers apprised of future developments. ■