**National Diabetes and Digestive and Kidney Diseases (NIDDK) Advisory Council Meeting**

**Division of Kidney, Urologic, and Hematologic Diseases Advisory Subcouncil Meeting**
**September 7, 2022**

**Advisory Council KUH Subcommittee Members:**

Dr. Iain Drummond (MDI Biological Laboratory)
Ms. Dawn Edwards (American Association of Kidney Patients)
Dr. Mark Nelson (University of Vermont)
Dr. Keith Norris (University of California at Los Angeles)
Dr. Susan Quaggin (Northwestern University [Subject Matter Expert])
Dr. David Penson (Vanderbilt University)
Dr. Kathleen Sakamoto (Stanford University)

**NIH/NIDDK/KUH Staff:**

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Ms. Neha Shah
Ms. Aliecia Shepherd
Dr. Victoria Spruance
Dr. Robert Star
Mr. Jonathan Teinor
Dr. Ken Wilkins

**Welcome and Introductions**

Dr. Star welcomed council members and attendees to the 220th KUH subcouncil meeting. Drs. Penson and Drummond led the motion to approve the meeting minutes from May subcouncil. Dr. Star noted that Dr. Quaggin will be serving as an Ad Hoc Councilor for Dr. Stewart this round. Additionally, Dr. Drummond will be rotating off the NIDDK Advisory Council at the end of the year. Dr. Star also introduced Esohe Irabor, a detail from the HHS's Office of Minority Health, who will be assisting NIDDK staff for several months.

**Upcoming Meetings and Workshops**

Dr. Star noted several upcoming meetings and workshops and commented that this information was available on the ECB for future reference.

**Update from the NIDDK meeting on Designing Interventions that Address Structural Racism to Reduce Kidney Health Disparities**

Dr. Greer detailed the need for this initiative based on the marked racial inequities in health and health care, including reduced access to care, receipt of poorer quality of care, and greater risk of kidney disease and progression to kidney failure among racial and ethnic minority populations. Structural racism is widely recognized as a fundamental cause of these inequities and is defined as the "Totality of ways in which societies foster racial discrimination, through mutually reinforcing inequitable systems (in housing, education, employment, earnings, benefits, credit, media, health care, criminal justice, and so on) that in turn reinforce discriminatory beliefs, values, and distribution of resources, which together affect the risk of adverse health outcomes." This leads to greater exposure to adverse social determinants, such as housing insecurity, food insecurity, inadequate health care, and other adverse social and living conditions that negatively impact health and lead to poor kidney disease outcomes.

Dr. Greer displayed a conceptual framework for the root causes of kidney health disparities and commented that this illustrates how structural racism contributes to stark and long-standing inequities in health and health care for people with kidney disease, including:

- the upstream structural determinants, which include inequitable health care policies;
- the midstream social determinants, such as neighborhood environment that shapes health; and
- the downstream effects these social determinants have on the lives of individuals at risk of and living with kidney disease.

To achieve health equity for people with kidney disease, interventions are needed that target all of these levels, the upstream approaches that aim to dismantle structural racism, as well as interventions to mitigate the adverse social determinants of health that result from structural racism. The NIDDK's "Designing Interventions that Address Structural Racism to Reduce Kidney Health Disparities," held on February 24-25, 2022, sought input from experts, individuals living with kidney disease, community members, other government agencies, and other key stakeholders to identify actionable research trial questions for interventional research that address structural racism.

Key needs for future interventional research included:

- Apply an anti-racism lens
- Promote structural interventions
- Target multiple socioecological levels and domains of influence
- Promote authentic community and stakeholder engagement
- Improve data collection
- Advance health equity through new health care models

Potential interventions included:

- Kidney Navigators (e.g., peers, community health workers, Promotoras)
- New models of care delivery (e.g., mobile clinics, integration of social/medical care)
- Payment/provider incentive reform
- Enhance telehealth/broadband access to enhance access to care
- Expand overall health care access
- Food environment interventions (e.g., tax credits; zoning laws)
- Provide food, housing, and income support to pregnant mothers

Based on feedback from the workshop, KUH staff developed the following two funding announcements to move research forward in this area:

- RFA-DK-22-014: Interventions that Address Structural Racism to Reduce Kidney Health Disparities – (U01- Clinical Trial Required)
- RFA-DK-22-015: Interventions that Address Structural Racism to Reduce Kidney Health Disparities – Research Coordinating Center (U24 - Clinical Trial Not Allowed)

Dr. Greer commented that the goal of these funding announcements are to support a Consortium comprised of a Research Coordinating Center (RCC) and up to 6 Intervention Sites working collaboratively to:

- Design and conduct community-engaged clinical trials to test novel interventions that dismantle or mitigate the effects of structural racism that contribute to kidney health disparities
- Foster research collaborations between investigators, people living with kidney disease, community-based organizations, and other key stakeholders.

As a key funder for kidney research, NIDDK has a responsibility to address structural racism and support interventional research that aims to dismantle or mitigate the effect of this upstream driver of inequities in health. Dr. Greer added that these funding announcements are just one example of the many steps NIDDK is taking towards achieving that goal. A meeting summary from this workshop is available on the NIDDK's website.

Councilors provided the following feedback:

- Dr. Quaggin noted strong enthusiasm for this initiative to advance kidney health and queried if this effort could be partnered with the Community Partnerships to Advance Science for Society (COMPASS) program. Dr. Greer noted COMPASS is an NIH-wide program and added that COMPASS is designed to conduct structural interventions that are disease agnostic and not limited to kidney research.
- Ms. Edwards expressed support for this important initiative and commented that she enjoyed the opportunity to participate as a patient representative in this workshop.
- Dr. Norris commented that this is an opportunity to look to consider what race and ethnicity means in society and how these differences manifest into different medical conditions. He added that this will help efforts in other areas of science in NIDDK as the current research areas are suboptimal.
- Councilors noted the need to address treatment as well as social factors such as housing insecurity. Dr. Norris suggested that NIDDK staff also consider how the pathways that affect health outcomes relate to different domains within the social determinants of health (SDoH) construct. He commented that this requires a multilevel solution to a multilevel problem. Dr. Norris noted pharmacotherapies could have an impact to change educational funding at an international level. Ms. Edwards commented that while pharmacotherapies will help suppress the need for transplant, society has a responsibility to address structural racism such as food deserts and housing insecurity. Ms. Edwards also commented that she was pleased with interventions developed at this workshop and noted that she would like to see community level solutions that address SDoH.
- Dr. Drummond commented on the need to change the structure of society as health effects can be multi-generational. He advised that staff also consider the long-term propensity for disease in individuals as well as consider how basic biology studies may intervene in the long run.
- Dr. Nelson commented that identifying pathways to structural racism is a good approach to this problem and added that therapeutics enable researchers to observe basic biology in

individuals. Dr. Kimmel commented that therapeutics have to be accessible to the population in need.

**Councilor Presentations**

Dr. Sakamoto shared her recommendations for projects, ideas, and initiatives for KUH in hematology. Her suggestions for integrating hematology research with other KUH topics included:

- Epigenetic changes in hematopoiesis of chronic renal failure patients.
- Hematopoietic consequences of NIDDK-relevant organ systems

Dr. Sakamoto commented that initiatives involving research concepts such as health disparities and clonal hematopoiesis/MDS would be useful as well as concepts which support research in hematopoiesis and bone marrow failure (BMF). She also emphasized the importance of developing better disease models for hematopoietic diseases and suggested creating a consortium to bring individuals of different expertise together to discuss how to build better in vitro models to reflect human disease.

Additional suggestions for research initiatives in hematology included:

- The bone marrow microenvironment (e.g., Genetic models to determine how various components of the bone marrow microenvironment influence stem and progenitor cell growth and engraftment - Hematopoietic Stem Cell Niche (NOT-DK-17-016)
- The importance of hypoxic bone marrow ME in regulating stem and progenitor cell functions
- Mechanisms of stem cell homing and expansion – Hematopoietic Stem Cell Niche (NOT-DK-17-016)
- Microbiome and impact of chronic inflammation on stem cells. Including how diabetes and obesity influences stem cell functions – Hematopoietic Response to Stress (NOT-DK-19-028)
- Post-translational modifications, nature of TF complexes, structure of these complexes, use of Cryo-EM – new NIDDK program for grants on nuclear architecture?

Dr. Sakamoto also commented on the dedication of NIDDK Program Officers, noting that trainees receive helpful advice and direction from program staff, and she expressed strong enthusiasm for the SHINE program. She remarked that it would be helpful to establish more clear criteria when differentiating whether an applicant should apply to NIDDK versus NHLBI. She also suggested that staff hold more hematology-focused workshops, consider using the R35 mechanism, and focus on multi-PI grants between Ph.D.s and M.D.s.

In terms of training, Dr. Sakamoto suggested efforts that span both nonmalignant and malignant hematology as most hematologists do both in clinical practice, as well as expanding the spectrum of hematologic diseases. She commented that training in both nonmalignant and malignant areas would expand training opportunities, grants in the future, and would align with most hematologists in training and their clinical interests. In closing, Dr. Sakamoto noted it would also be helpful to extend K support with benchmarks during the training period.

Staff and councilors provided the following comments:

- Dr. Star noted the need for better communication when advertising KUH programs and FOAs, while noting that the new Tool Development R21s have been well received. He

also commented that a previous partnership with NCI to expand nonmalignant urologic research did not benefit NIDDK and was heavily focused on cancer.
- Dr. Roy commented that, in the long run, an investigator may have more success recompeting an R01 than applying for the R35.
- Dr. Nelson also commented that KUH Program Officers communicate well with grantees and added that the R35 mechanism also has limitations.

Dr. Nelson remarked that research questions remain on sensing bladder fullness and patient perception of lower urinary pain. Dr. David Julius received the Nobel Prize for his identification of a gene that makes cells sensitive to capsaicin. This gene codes for the TRPV1 receptor, an ion channel activated by temperature. Other temperature-sensing ion channels were discovered, including TRPM8, which is activated by cold temperatures and was identified using menthol (a cooling compound found in mint). Following this advance, Dr. Ardem Patapoutian received the Nobel Prize for his discovery of touch receptor like Piezo 1 and Piezo 2. The following are roles of TRPV1 and Piezo channels in the urinary bladder:

- Sensory innervation from the bladder is conveyed by myelinated low threshold Aδ fibers and unmyelinated high threshold C fibers carried in the pelvic, hypogastric and pudendal afferent nerves.
- TRPV1 channels are expressed in C fibers and are likely involved in pain sensation. TRPV1 channels are also expressed in arteriolar smooth muscle in the bladder.
- Piezo2 channels are expressed in sensory nerves and urothelium. Piezo1 is expressed in the urothelium and vascular endothelium.

However, further research in this area did not explain how mice and humans deficient in Peizo2 channels are still able to void. Although research has advanced our understanding in this area, he noted that a challenge remains in the development of selective therapeutics for targets that are expressed in many cell types.

Dr. Nelson also provided the following suggestions for trans-KUH areas of research:

- GU fibrosis: Therapies/clinical trials to reverse lower urinary tract fibrosis (kidney, ureter, bladder, prostate, penis)
- GU smooth muscle dysfunction: Therapies/clinical trials to improve lower urinary tract smooth muscle dysfunction (ureter, bladder, prostate, penis)
- Urolithiasis: Advances in etiology and prevention to achieve personalized medicine of pediatric and adult cohorts

Dr. Nelson commented that while these three topics are not novel, they remain great research needs in urologic areas that have lost some momentum. In his closing remarks, Dr. Nelson thanked the NIDDK Advisory Council for the opportunity to participate and for the NIDDK's commitment to urology.

Dr. Penson offered his recommendations on clinical research opportunities for benign urologic conditions:

- Diversity and health equity
    - Very few studies exploring health equity in benign urologic disease
    - Racial differences in benign and malignant prostate disease have been hypothesized to exist.
        - Age-specific PSA ranges
        - Incidence of prostate cancer by race

    - Opportunities exist to explore differences in biology of disease, access to care and relative effectiveness of interventions related to race/ethnicity, socioeconomic status, sexual orientation, etc.
- Stress Urinary Incontinence (SUI)
    - SUI remains significant public health problem
    - Care of women with SUI is currently stalled – in limbo largely because of issues due to surgical mesh:
        - Some potential from PLUS network on prevention, but this does not help with current care
        - Prior RCT networks are inactive (UITN, PFDN)
        - Ongoing research on stem cell therapy with uncertain translational applications to humans
        - Women (and providers) are turning to uncertain or unproven therapies as alternatives (e.g., Vaginal laser therapy as one example)
    - Need greater representation of racial/ethnic diversity in SUI research
        - Gonzalez et al. (2022): Underrepresentation of Racial and Ethnic Diversity in Research Informing the American Urological Association/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction Stress Urinary Incontinence Guideline. *Urology* (https://doi.org/10.1016/j.urology.2021.08.038)
- Neurogenic lower urinary tract dysfunction
    - Very significant public health issue
        - large healthcare system and personal burdens
        - patients are most disadvantaged socioeconomically and underserved
    - Upcoming NIDDK neurobiology workshop is a good start
    - Recent AUA Guidelines on NLUTD identified many knowledge gaps
        - Needed advances in role of neuromodulation
        - Role of urinary diversion and reconstruction
        - Unanswered questions around condition-specific patient assessment and patient-reported outcomes (PROs)
- Chronic Prostatitis/Chronic Pelvic Pain
    - AUA is cautiously developing clinical guidelines in this condition
        - This has been deferred numerous times due to lack of level I evidence
        - Significance felt to be so great that this could no longer be deferred
        - Unclear if guidelines will be useful given the lack of evidence and likely need to rely expert opinion
    - NIDDK has sponsored the MAPP network and other initiatives in this domain
        - Numerous important publications and research tools have come out of these networks
        - Need for randomized/well-designed studies of clinical interventions is pressing
- Urinary Tract Infections (UTIs)
    - One of the most significant public health issues
    - Prevalence is high/ common
    - antibiotic resistance growing crisis
    - Recent advances in urine microbiology (urinary microbiome) and advanced urine testing, but still large gaps as to how this relates to UTI and clinical care
    - How do we use these tools and improve outcomes?
    - AUA Guidelines on UTI identified significant gaps in knowledge, including several related to uncertainties for management

    - Associations with disparities (racial/ethnic, social, etc.) largely unknown
- Urinary stone disease
    - Utilizing pragmatic trials/collaborative networks to improve patient outcomes related to surgical and preventative interventions
    - Examples include conducting comparative effectiveness studies on ureteral stent placement after ureteroscopy; evaluating strategies to improve adherence to dietary and medical preventative therapy; studying the impact of stone treatment in patients with recurrent UTIs; and determining optimal follow-up strategies after treatment.
    - Understanding the natural history of urinary stone disease
    - Examples include conducting prospective observational studies on watchful waiting versus early intervention for asymptomatic stones; studying mediators for kidney stone recurrence; studying patterns of recurrence and manifestations of recurrence; and studies that examine impacts on bone health and renal function over time.

Staff and councilors provided the following comments:

- Dr. Hattangadi commented that Piezo1 mutations are responsible for hereditary Xerocytosis, a congenital hereditary hemolytic anemia.
- Dr. Nelson noted UTIs are accompanied by dementia in the elderly population and added that there is an interesting crossover between urology and dementia research. Dr. Penson commented that this would be an interesting study as little is known about UTIs.
- Dr. Penson suggested that NIDDK staff partner with professional societies and the clinical community to discuss a trial design for stress incontinence. He added that it would also be beneficial to recruit expertise outside of KUH science to hear diverse perspectives on what works and what does not work.
- Dr. Nelson commented that it was helpful for him to serve as an EEP member to hear presentations from investigators on this research topic.
- Dr. Quaggin commented that the U2C program has been helpful in gathering ideas from a diverse range of investigators.

Dr. Quaggin opened her presentation by commenting that funding levels for kidney research are low and added that patient voices often go unheard. However, she detailed two opportunities that remain in this space:

- recent major advances in treatments (flozins, non-steroidal MRAs, CKD-epi 21) and
- a commitment from the White House to reduce health disparities.

She remarked that there is a need to recruit new expertise into kidney research and focus on building the pipeline, partnering with patients, and using diversity/inclusiveness as a scoreable component. Within discovery research, new platforms are needed to study omics, genetic, and atlases such as The GenitoUrinary Development Molecular Anatomy Project (GUDMAP), as well as the need to enhance sharing of human datasets such as the Kidney Precision Medicine Project (KPMP).

In conclusion, she detailed several suggestions using a multipronged approach:

- Pipeline – macro: partnerships (early programs, foundations), change in policy (foreign trainees)
- Pipeline – micro: bioinformatics training grant awards to increase capacity; partner with non-traditional institutes (mandate training in a kidney project in bioengineering/chemistry etc. – joint mentorship)

- Specific research areas to advance kidney health (augmented intelligence, gene editing, mRNA technologies, cell-specific targeting)
- Transformative funding – (increasing application submissions to increase payline is incremental) - ARPA-H? Special allocations?
- Exciting new programs (U mechanisms, U2C/TL1 training grants) – essential to monitor impact, success & communicate to community

Dr. Drummond thanked Dr. Quaggin for her presentation and commented further on specific research areas to advance kidney health, noting that NIDDK has significantly invested in molecular phenotypes and transcriptional profiling to better understand kidney disease. He listed several questions for study within the following existing consortia:

- ReBuilding a Kidney (RBK) has identified productive/non-productive kidney tubule repair pathways as well as pathways promoting kidney organoid maturation and function. How will we leverage this for therapy?
- KPMP is generating exciting new data on disease specific markers with a mission: "to identify key molecular pathways, gene targets, diagnostic markers to redefine and sub-stratify AKI and CKD; and to identify possible targets for intervention." Beyond diagnostics, how will we intervene in kidney disease?
- GUDMAP, RBK, KPMP: NIDDK has invested in data hubs and bioinformatic analysis to make large scale data sets publicly accessible. How will we make all this data actionable as therapy?

Dr. Drummond also commented that NIDDK has succeeded in finding the genetic causes of heritable kidney disease such as Alport syndrome, Polycystic Kidney Disease (PKD), cystinosis, and Focal Segmental GlomeruloSclerosis (FSGS), and he suggested further study to see if genetic disease pathology can be reversed. Dr. Drummond commented that, once a genetic defect is reversed, the regenerative processes can restore normal function and cited two papers below:

- Dong K, Zhang C, Tian X, Coman D, Hyder F, Ma M, Somlo S. Renal plasticity revealed through reversal of polycystic kidney disease in mice. Nat Genet. 2021 Dec;53(12):1649-1663.
- Lakhia R, Ramalingam H, Chang CM, Cobo-Stark P, Biggers L, Flaten A, Alvarez J, Valencia T, Wallace DP, Lee EC, Patel V. PKD1 and PKD2 mRNA cis-inhibition drives polycystic kidney disease progression. Nat Commun. 2022 Aug 15;13(1):4765.

In closing, Dr. Drummond commented that the challenge is how to leverage our assets and build synergies by targeting a broad spectrum of kidney disease with genetic and regenerative therapies such as:

- Molecular medicines: gene therapy, mRNA therapies, miRNA therapies?
- Delivery systems: kidney specific AAV, lentivirus, nanobodies, nanoparticles; introduce genes or CRISPR approaches in a kidney cell targeted fashion; the kidney lags other organs.
- kidney cell-targeting gene delivery systems

Dr. Drummond noted the importance of making new therapies in this area accessible to all kidney patients and thanked staff for the opportunity to present.
Staff and councilors provided the following comments:

- Dr. Star commented an NIH Data Scholar will allocating part of his time in KUH to integrate datasets within KUH consortia, such as KPMP and added that KUH staff are working on efforts directed in augmenting intelligence. There will be two papers on this research that will appear in next iteration of the NIDDK's Recent Advances & Emerging

Opportunities document. Additionally, he noted work with CMS to pay for genetic engineering efforts in Sickle Cell Disease as well as ongoing discussions with CMS staff regarding payment reimbursement and health equity issues.

- Dr. Kimmel noting that KUH is moving towards having a Community Advisory Council/Patient Advisory Group in all NIDDK cooperative agreements. Currently, these agreements already exist in the KPMP, APOL1 Long-Term Kidney Transplantation Outcomes (APOLLO), Caring for OutPatiEnts after Acute Kidney Injury (COPE-AKI), and Hemodialysis Opioid Prescription Effort (HOPE) Consortium consortiums, among others.

**KUH Closed Session**

Dr. Star commented on the importance of confidentiality during closed session. Council members approved several closed business items.