National Diabetes and Digestive and Kidney Diseases (NIDDK)
Advisory Council Meeting
Division of Kidney, Urologic, and Hematologic Diseases
Advisory Subcouncil Meeting
January 30, 2020

Advisory Council KUH Subcommittee Members:
Dr. Toby Chai (Boston Medical) *ad hoc*
Dr. Iain Drummond (Harvard Stem Cell Institute (HSCI)
Dr. Lisa Guay-Woodford (Children's Hospital)
Mr. Richard Knight (American Association of Kidney Patients)
Dr. David Penson (Vanderbilt University) *ad hoc*
Dr. Kathleen Sakamoto (Stanford University) *ad hoc*
Dr. Ian Stewart (Commissioned Corps of the US Public Health Service)

NIH/NIDDK/KUH Staff:

Dr. Kevin Abbott
Dr. Julia Barthold
Dr. Tamara Bavendam
Dr. Terry Bishop
Dr. Kevin Chan
Dr. Sandeep Dayal
Dr. Patrick Donohue
Dr. Daniel Gossett
Dr. Xiaodu Guo
Dr. Jason Hoffert
Dr. Deborah Hoshizaki
Ms. Julia Jackson
Dr. Chris Ketchum
Dr. Paul Kimmel
Dr. Ziya Kirkali
Dr. Karl Malik
Dr. Christine Maric-Bilkan
Dr. Susan Mendley
Ms. Saadia Miran
Dr. Chris Mullins
Ms. Van Nguyen
Ms. Jenna Norton
Dr. Afshin Parsa
Ms. Aretina Perry-Jones
Dr. Tracy Rankin
Dr. Cindy Roy
Dr. Anna Sadusky
Dr. Ivonne Schulman
Ms. Aliecia Shepherd
Dr. Ken Wilkins

1. Welcome and Opening Remarks

Dr. Star welcomed councilors and participants to the 212th KUH subcouncil meeting. Council members approved the minutes from September 2019.

2. FY2019 Portfolio Analysis

Dr. Ketchum provided an overview of the 2019 KUH portfolio. KUH total awarded dollars are lagging NIDDK, and more ESIs are needed.

- Kidney applicant pool is growing, but they submit fewer R01s for fewer dollars… so they are losing share.
- Urology applicant pool is flat, and they submit fewer R01s for fewer dollars. Several new career development (K) awards is promising.

- Hematology is still losing PIs, applications and dollars (mostly to NCI and HL).
- KUH R01 success rates are strong, but R01 dollars and ESI applications are lagging.

Councilors and staff offered the following feedback:

- Dr. Guay-Woodford queried if the U01 mechanism was successful in getting people to submit R mechanism applications. Dr. Ketchum responded that KUH has seen some success with KPMP, CRIC, APOLLO, and HEAL, which have added large groups of investigators that are new to KUH. KUH will track the data to see if the new investigators will stay. However, previous analyses of large initiatives are mixed in terms retaining people.
- Dr. Guay-Woodford also queried if this was an intentional strategy to pull people in for team science using the large consortiums. If so, she asked our next steps would be, and what are the carrots to build on their team science that would move into an R01. She also inquired if KUH had a plan to make this more successful and stated that investigators are looking for the "Snap, Crackle and Pop." Dr. Ketchum stated that KUH is aware of the numbers and is working to attract, engage, and retain people to submit successful R01 applications. Dr. Kimmel added that the HOPE consortium receives funding as part of a common Building 1 initiative. This initiative brought NIDDK PIs into a collaboration with opioid scientists, pain doctors, behavioral scientists, and other doctors. Through this collaboration, NIDDK PIs are positioned to engage other PIs to continue to look into areas within DK-interest. Dr. Ketchum added that another strategy is to recruit junior people into the labs of these large consortium project to foster their interest in KUH science.
- Dr. Drummond inquired if KUH is seeing greater success from junior level investigators who transition from a large consortium to the R mechanisms. Dr. Star commented that a lot of time elapses between the time a new investigator is funded through a large consortium, until the time they successfully transition to the R01 phase. He noted that this transition can take as long as 10 years. He noted that the SUITOR program is designed to attract and retain new investigators to the urology portfolio. Dr. Rankin added that MAPP, CRIC, and NEPTUNE are generating K applications. Dr. Ketchum mentioned that the consortiums also generate resources to seed R01s. Dr. Drummond stated that he felt recruitment begins with the study section and how study sections approach new innovative science. Dr. Drummond noted he felt that the program officers in KUH need to communicate these concerns to SROs to encourage new initiatives and investigators. Dr. Ketchum agreed and stated that low R01 paylines likely exacerbate this issue. .
- Dr. Drummond advised KUH to provide adequate focus on younger investigators because they are greater risk takers. Dr. Ketchum responded that the R25 mechanism is designed for younger investigators who are geared toward taking risks. He also stated that the average age of someone getting their first R01 is in their 40s.
- Dr. Guay-Woodford stated that investigators are drawn by the money and the excitement of the field and queried if dissemination efforts are reaching junior PIs. Dr. Guay-Woodford referenced SHINE as an example of how the PIs normally follow money. She emphasized the importance of mentorship and commented that peer-to-peer mentors can bring together the ESIs who are successful.
- Dr. Guay-Woodford reiterated that KUH should not just focus on training, but on the new people making successful transitions. Though KUH is doing this with the R25, Ks and Ts, this effort should be expanded to encourage a new of community among new investigators. Dr. Rankin praised Drs. Bavendam and Mullins for their attempt to address this need by creating CARIBOU, which brings together urology center directors and career development program directors and fellows.

- The AUA representative commended the DK policy for giving ESI extra consideration with their first award but questioned how much support ESIs receive throughout their research and at the conclusion of their award. Dr. Ketchum responded that NIDDK awarded ESIs also receive a more generous payline at the time of their first competitive renewal.
- Dr. Penson mentioned the bottleneck of when the K ends and how KUH leverages the K99 mechanism. He feels that at the period after the K99 ends, many PIs have a hard time receiving a fundable score. He added that the R03 will be very helpful for the physicians to extend the Ks and provide hope to secure funding. Dr. Rankin added that the R03 is available to provide the extra support, and highlighted the new program created by NIDDK to provide extra support to women who may have children and need funding to ensure they continue working in research.
- Dr. Drummond stated that innovation should be a primary focus for who applies to the tool development R21. He added that the next generation is more entrepreneurial, and we need to tap into that mindset. Dr. Ketchum commented that Dr. Gossett has started to address that entrepreneurial shift in his new R21 and R25 initiatives.

3. Improving interoperability of Patient-Centered Data for Research and Care

Ms. Jenna Norton began her presentation by discussing the potential of electronic (e-) care plans to improve availability of data for research and care. The e-care plan uses data standards to enable access to/sharing of comprehensive, person-centered information across the healthcare team, including the patient and family caregivers. Thus, the e-care plan may overcome barriers to care coordination and data sharing across healthcare, community, and research settings in the current health information technology landscape, characterized by poor interoperability of data. Perhaps most importantly, an e-care plan provides patients with a comprehensive approach to decision making based on information provided by all their providers.

In October 2015, NIH held a meeting focused on "using health information technology to identify and manage CKD populations." Ms. Norton summarized six priority activities identified by participants:

- Electronic care plan for CKD
- Tools to engage patients in the generation and consumption of data
- A "killer app" to support CKD patient self-management
- Electronic dashboards to facilitate CKD data input and review
- Business case to justify investment in CKD population management infrastructure
- Computable phenotypes to identify CKD patients –especially high risk patients

Shortly after the NIH meeting in 2015, the National Kidney Disease Education Program (NKDEP) developed the CKD Care Plan Working Group in January 2016. To create an e-care plan with input from the broader community, NKDEP engaged a working group of stakeholders with different vantage points which included people with CKD, their family caregivers, internists/primary care providers, nephrologists, public health professionals, health informaticists and geriatricians.

The CKD Care Plan working group efforts included interviews with patients about their preferences for data access and exchange, development of personas and scenarios describing data needs and priorities from various perspectives (patients, caregivers, clinicians) and across numerous situations, and input from a broad set of stakeholders. Personas and scenarios are tools used in software development. They are fictional but realist people and situations that represents the challenges, needs, and preferences of potential software users. Ms. Norton shared one of the personas developed by the working group, "Betsy Johnson." The persona illustrated patient challenges in the current health information technology

landscape and preferences for what a care plan should include. Outputs from the CKD working group included 11 personas (including Betsy), a set of more than 300 data elements mapped to common clinical terminologies, and a mock-up of a user-friendly, clinician-facing display of the data elements. Key lessons learned from the CKD e-care plan project included that an e-care plan must be a dynamic dataset rather than a static document to enable user-centered displays and provide a balance between brief & comprehensive information, and that a single disease-based approach to e-care planning is untenable in the context of multiple chronic conditions – which are common in people with CKD.

Following the NKDEP effort, Ms. Norton discussed expanding the NIDDK CKD e-care plan, in partnership with the Agency for Healthcare Research and Quality (AHRQ) and with funding from the Assistant Secretary for Planning and Evaluation, to address multiple chronic conditions, including select cardiovascular diseases, type 2 diabetes, and chronic pain. This project will rely on input from a broad set of stakeholders, including two NIDDK Councilors: Richard Knight, MBA and Ian J. Stewart, MD. The project, launched in 2019 and expected to be completed in 2023, aims to develop:

- Standardized data elements for diabetes, cardiovascular disease & chronic pain (building off CKD data elements)
- Clinical information models/FHIR profiles to specify data structure & semantics for storing all data elements in health IT systems
- Pilot tested e-care plan application & implementation guide that integrates with the EHR to pull, share & display key patient data

Ms. Norton concluded by acknowledging that the Multiple Chronic Conditions e-Care Plan Project is just one piece of a puzzle necessary for successful development and implementation of a comprehensive, patient-centered e-care plan. For example, in addition to this work, data elements and standards will need to be developed around numerous additional diseases and conditions, use of FHIR in research will need further exploration, more robust regional health information exchanges must be developed, and use of common clinical terminologies (rather than internal data standards) must become more widespread.

Councilors and staff offered the following feedback:

- Dr. Guay-Woodford expressed enthusiasm and commented that this will be helpful for children with PKD, CKD, and other rare diseases. These patients travel substantially to participate in research trials. She suggested that the e-care plan encompass children as well as adult patients. Ms. Norton agreed that pediatric patients will be an important future extension of this work. This future vision of a comprehensive e-care plan spans the life course, from prenatal through end-of-life care.
- Dr. Stewart stated that this effort addresses the major issue that has impacted the Veteran's Administration (VA) for years. In particular, Dr. Stewart noted the challenge of creating a system to store all of the necessary data in a usable format to improve patient care.
- Dr. Drummond stated that individual access to multiple clinicians is valuable, and the model presented by Ms. Norton is similar to models used within his current health care system. Ms. Norton added that within healthcare network data exchange is less problematic and several integrated or networked health systems have joined their systems with an agreement to use the same infrastructure to ensure ease of data sharing and communication. However, such practices are still not a widespread and do not address data interoperability challenges when individuals seek care outside of the small networks.
- Mr. Knight added that this direction is where technology seems to be trending, and he encouraged NIDDK to prioritize these advancements. He also noted that, due to costs and implementation,

this is not a priority within the private sector. Mr. Knight expressed gratitude for the various stakeholders who have promoted this program.

Dr. Star concluded the discussion by reiterating the advantages and value of e-care plans to improve person-centeredness of care.

4. Councilor Initiative Presentations

Dr. Ian Stewart began his talk with updates in the following nephrology clinical trials: CREDENCE, KALM-1, and PIVOTAL. The Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) was a double-blind, randomized trial. Patients with type 2 diabetes, albuminuria (ratio of albumin [mg] to creatinine [g], >300 to 5000), and chronic kidney disease (CKD; glomerular filtration rate (GFR) of 30 to <90 ml per minute per 1.73 m2 of body-surface area) received the oral SGLT2 inhibitor canagliflozin (100 mg daily) or placebo. All patients were treated with renin–angiotensin system blockade. The primary outcome was a composite of end-stage kidney disease (ESKD; dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes. The trial was stopped early after a planned interim analysis on the recommendation of the data and safety monitoring committee. At that time, 4401 patients had undergone randomization, with a median follow-up of 2.62 years. The relative risk of the primary outcome was 30% lower in the canagliflozin group than in the placebo group. Dr. Stewart noted that a consistent benefit was seen in secondary outcomes and across subgroups. Unanswered questions include the mechanism of action of the drug and efficacy in non-diabetic CKD and Stage 4 CKD. Of all three trials, the CREDENCE trial provided the most significant results. Dr. Stewart noted the following citation for this study:

- Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW; CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019 Jun 13;380(24):2295-2306.

Following his discussion of CREDENCE, Dr. Stewart discussed the Study to Evaluate the Safety and Efficacy of CR845 in Hemodialysis Patients with Moderate-to-Severe Pruritus (KALM-1) trial. In this randomized, double-blind, placebo-controlled, phase 3 trial, patients undergoing hemodialysis who had moderate-to-severe pruritus received either intravenous (IV) difelikefalin (0.5 μg per kilogram of body weight) or placebo three times per week for 12 weeks. The primary outcome was the percentage of patients with an improvement (decrease) of at least 3 points from baseline at week 12 in the weekly mean score on the 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS; scores range from 0 to 10, with higher scores indicating greater itch intensity). The secondary outcomes included the change from baseline in itch-related quality-of-life measures, the percentage of patients with an improvement of at least 4 points in the WI-NRS score at week 12, and safety. A total of 378 patients underwent randomization, with 51.9% in the difelikefalin group reaching the primary outcome as compared with 30.9% in the placebo group. Diarrhea, dizziness, and vomiting were more common with difelikefalin. Dr. Stewart noted the following citation for this study:

- Fishbane S, Jamal A, Munera C, Wen W, Menzaghi F; KALM-1 Trial Investigators. A Phase 3 Trial of Difelikefalin in Hemodialysis Patients with Pruritus. N Engl J Med. 2020 Jan 16;382(3):222-232.

Lastly, Dr. Stewart described the PIVOTAL trial, a multicenter, open-label trial with blinded end-point evaluation that randomly assigned dialysis patients to receive either high-dose iron sucrose, administered IV in a proactive fashion (400 mg monthly, unless the ferritin concentration was >700 μg per liter or the transferrin saturation was ≥40%), or low-dose iron sucrose, administered IV in a reactive fashion (0 to 400 mg monthly, with a ferritin concentration of <200 μg per liter or a transferrin saturation of <20% being a trigger for iron administration). The primary end point was the composite of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death, assessed in a time-to-first-event analysis. A total of 2141 patients underwent randomization (1093 to the high-dose group and 1048 to the low-dose group). The median follow-up was 2.1 years. Patients in the high-dose group received a median monthly iron dose of 264 mg (interquartile range [25th to 75th percentile], 200 to 336), as compared with 145 mg (interquartile range, 100 to 190) in the low-dose group. The high-dose IV iron regimen administered proactively was superior to the low-dose regimen administered reactively and resulted in lower doses of erythropoiesis-stimulating agent being administered. Dr. Stewart focused on some of the potential side effects and questioned whether iron therapy could improve some of the fatigue and other symptoms reported in dialysis patients. Unanswered questions remain, including effect of iron therapy on mortality and its role in anemia management in CKD patients. Dr. Stewart noted the following citation for this study:

- Macdougall IC, White C, Anker SD, Bhandari S, Farrington K, Kalra PA, McMurray JJV, Murray H, Tomson CRV, Wheeler DC, Winearls CG, Ford I. PIVOTAL Investigators and Committees. Intravenous Iron in Patients Undergoing Maintenance Hemodialysis. N Engl J Med. 2019 Jan 31;380(5):447-458

The second focus of his presentation was the use of artificial intelligence (AI) and its utility in predicting acute kidney injury (AKI). Dr. Stewart discussed one Veterans Affairs study that developed a deep learning approach for continuous risk prediction, building on recent work that models adverse events from electronic health records and using AKI—a common and potentially life-threatening condition—as an example. The model was developed on a large, longitudinal dataset of electronic health records that cover diverse clinical environments, comprising 703,782 adult patients across 172 inpatient and 1,062 outpatient sites. This model predicted 55.8% of all inpatient episodes of AKI, and 90.2% of all AKI that required subsequent administration of dialysis, with a lead time of up to 48 h and a ratio of 2 false alerts for every true alert. In addition to predicting future AKI, this model provided confidence assessments and a list of the clinical features that are most salient to each prediction, alongside predicted future trajectories for clinically relevant blood tests. Below is a citation for this study:

- Tomašev N, Glorot X, Rae JW, Zielinski M, Askham H, Saraiva A, Mottram A, Meyer C, Ravuri S, Protsyuk I, Connell A, Hughes CO, Karthikesalingam A, Cornebise J, Montgomery H, Rees G, Laing C, Baker CR, Peterson K, Reeves R, Hassabis D, King D, Suleyman M, Back T, Nielson C, Ledsam JR, Mohamed S. A clinically applicable approach to continuous prediction of future acute kidney injury. Nature. 2019 Aug;572(7767):116-119.

Dr. Stewart noted that this data structure is unique to the VA and queried how clinicians could use this information. He also discussed the use of AI for renal biopsy pathology assessment and how slides can be scanned and quickly analyzed by AI. He commented that AI could help PIs use already identified biomarkers to predict subsequent outcomes. To conclude his presentation, Dr. Stewart noted that, long-term, this technology will provide tools to aid renal pathologists, predict patient response to treatment, improve standardization for clinical trials, enable more personalized therapies, and discover previously unrecognized associations. AI has the capability to move the field forward.

Dr. Star thanked him for his presentation and stated that Dr. Will Cefalu in DEM is interested in becoming an ad hoc member of KUH because of his interest in kidney disease. He also noted that KPMP PIs are incorporating the use of AI and using a more interactive system to find cells of interest. Dr. Kimmel added that KPMP will have a tremendous amount of pathology, as well as omics, metabolomics, and genomics data, which will be valuable to use in machine learning. Dr. Star concluded by adding that KUH is building digital repositories and anticipates use of AI more frequently in the future.

Following Dr. Star's introduction, Dr. David Penson began a discussion on where to focus research in benign urology. Dr. Penson praised NIDDK for the various resources available through LURN and MAPP and stressed the importance of studying voiding dysfunction, pelvic health, BPH, stone disease, and the associated neuroscience of these underlying issues. Due to the heavy public health burden, Dr. Penson commented that KUH should focus on primary prevention as opposed to treatment of urologic conditions. Currently, most of urology research focuses on treatment as treatment is profitable. Dr. Penson commented that voiding dysfunction and pain are more potentially related than what has been investigated. This could be accomplished by leveraging the existing MAPP and LURN networks. He suggested combining the datasets between LURN and MAPP and recommended studying different phenotypes and biospecimens together. If the PLUS consortium data can be analyzed, it will allow us to look at this in a very conclusive way. Additionally, Dr. Penson stated that despite similarities of pain and voiding symptoms in men and women, the labeling has traditionally been different.

Dr. Penson shifted his initiative focus to urinary stone disease and stated that this is a heavy public health burden. Stone disease research should focus on primary prevention as this disease requires large treatment expenditures each year. Although urinary stones are a very common problem, research beyond hydration for these patients is lacking. Dr. Penson recommended considering a study to investigate the impact of diet on kidney stones. Dr. Penson also stated the need to understand the basic science and commented that it has to be feasible and scalable. For example, a study that would measure the impact of diet and medications in high risk patients would be very interesting.

Councilors and staff offered the following feedback:

- Dr. Chai commented that the urinary tract is more complicated than the individual person being studied, and a better understanding of voiding is needed.
- Dr. Mullins stated that lessons learned in MAPP have been helpful in the development of LURN by sharing protocols. He added that the clustering approaches to develop clinically relevant subgroups have been important for both networks and that the investigators talk often on calls and use the same methods.

Dr. Star thanked Dr. Penson and expressed enthusiasm to combine the LURN and MAPP datasets. Dr. Bavendam added that although the PLUS consortium is moving in a different direction, it will use one of the LURN questionnaires and will collect similar specimens.

Dr. Star introduced Dr. Sakamoto, who led a discussion on training the next generation of hematology investigators and addressing the training pipeline. Dr. Sakamoto noted she recruits field experts outside hematology (such as those in lysosomes and epigenetics) and enlists their expertise on hematology applications. Additionally, she facilitates mentorship opportunities between junior PIs and established PIs within her institution. She commented that this may encourage junior PIs to continue in hematology research and apply for DK support.

Dr. Sakamoto added that she is a K awardee and commented that it is critical to engage junior PIs in benign hematology research. She suggested adding bridge and diversity grants will be beneficial since

underrepresented minority and female applicants seek diversity supplements. Dr. Sakamoto commented that she learned of other research resources, such as the Loan Repayment Program, through her participation in the NIDDK Advisory Council. She stated that she will share this with other leaders in the community, so they are aware of the opportunities to encourage and retain junior PIs.

As a physician scientist, Dr. Sakamoto recommended more emphasis on the interactions between basic scientists and communication with patients. She also suggested an RFA for pre-clinical studies to screen for new molecules and testing new drugs in animal models and commented that this would benefit NIDDK. In addition, this may increase the number of SBIR projects to find cures for orphan diseases that are lacking due to less financial incentives.

Dr. Sakamoto also noted other emerging areas for hematology research, including genomics, predicting biomarkers, and understanding pathogenesis and using it to translate how it can be applied to human disease. She also added that metabolomics is a growing area that the nonmalignant hematology community is lacking.

Councilors and staff offered the following feedback:

- Dr. Bishop thanked Dr. Sakamoto for her talk and commented that it would be helpful to alert the community about the available resources. Dr. Bishop suggested publishing an article in a highly circulated hematology journal to engage younger PIs about NIDDK resources and opportunities.
- Dr. Roy commented that the NIDDK's partnership with the American Society of Hematology promotes NIDDK related research activities to the external community. However, one potential outreach issue is the number of MDs at ASH while most of KUH investigators are PhDs. She questioned Dr. Sakamoto of what other organizations can we partner with to reach these PhDs who represent the majority of the hematology portfolio. Dr. Sakamoto stated that she did not have any specific suggestions, but noted she felt that many in the community still are unaware NIDDK funds hematology research.

Dr. Star commented that, large groups such as the American Society of Nephrology, the American Society of Urology, and the American Society of Hematology, often hire senior MD personnel who may not be relatable to PhD researchers. He noted that KUH is seeking recommendations on who to engage for the basic science areas of our K, U, and H programs.

Closed Session

KUH program staff and councilors discussed several business items and candidates for special emphasis funding. Dr. Star thanked all of the council members and attendees for their feedback and adjourned the KUH Sub-council meeting.