National Institute of Diabetes and Digestive and Kidney Diseases

Individualizing Urinary Incontinence Treatment—Evolving Research Questions to Research Plans

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Executive Summary

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Welcome from the NIDDK Deputy Director

Gregory Germino, M.D., Deputy Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH)

On behalf of NIDDK Director Dr. Griffin P. Rodgers and Division of Kidney, Urologic, and Hematologic Diseases (KUH) Director Dr. Robert Star, Dr. Gregory Germino welcomed attendees to the second NIDDK workshop on Individualizing Treatment for Urinary Incontinence. He thanked participants for taking time from their busy schedules to attend the meeting and acknowledged the more than 40 early-stage investigators who attended a pre-meeting workshop on establishing a research career in benign urologic conditions. A report of the pre-meeting workshop will be made available on the NIDDK website. Noting the focus of today's workshop, to develop an interdisciplinary research plan for individualizing treatment for urinary incontinence (UI), Dr. Germino remarked on two key themes: (1) how to build the research teams and science needed to advance research in individualizing treatment for UI and (2) how to think differently about funding benign urology research.

The urology research community over the past several decades has seen major advances in the treatment of benign urologic conditions, which have been due partly to NIDDK investments. In fact, significant contributions to improve our understanding of lower urinary tract (LUT) physiology and the development of effective treatments to manage UI can be attributed to leading researchers, many of whom are present today. Despite these advances, many of the treatments are not successful in all patients. Further studies to identify ways to target the right treatments to the right patients, as well as new ideas on the science necessary to address this problem, are needed. In addition, ways to broaden the NIDDK research portfolio and move away from top-down approaches, including consortia-led clinical trials, are being investigated.

Dr. Germino noted that future UI research must study LUT function in the context of other organ systems, behavior, and social factors to develop ways to target treatments better. He emphasized that achieving these objectives will require new approaches to research, including a shift toward cross-disciplinary research approaches. Early cross-disciplinary research approaches may begin with multidisciplinary research, in which multiple researchers from different disciplines work sequentially to address a common problem, but must advance toward interdisciplinary approaches, in which researchers from different disciplines work jointly to address a common problem, and ultimately to transdisciplinary research, in which researchers from different disciplines work jointly to create new approaches to address a common problem. In addition, the NIDDK envisions moving toward more comprehensive research approaches in which efforts expand to include not only LUT biology, but also local and systemic biology, human behavior, mind and mental functioning, and social determinants of health.

Finally, the NIDDK hopes to broaden research ideas by building the investigator-initiated (R01) research pool for benign urology research. The R01 is the mechanism for crystalizing innovative concepts and enabling a wider range of research ideas to surface and advance. In addition, a robust R01 portfolio focused on benign urologic conditions will contribute to a more favorable payline for this research community. About 60 percent of the NIDDK budget supports R01s. Allocating funds to other initiatives (e.g., consortia) decreases the amount available for the R01 pool and makes the payline less favorable. Furthermore, the number of submitted R01s is used to gauge the importance of an area of science across the NIH, and a robust benign urologic conditions R01 portfolio may enable the NIH to re-establish the standing Urologic and Genitourinary Physiology and Pathology Special Emphasis Panel study section, thereby improving the quality of NIH review for researchers in this area.

In closing, Dr. Germino encouraged participants to focus on using their time at this meeting to build cross-disciplinary partnerships, get out of their comfort zones, and actively listen and communicate new ideas—even if those ideas are not fully formed. He expressed appreciation to the organizing committee for facilitating the meeting.

Reference

1. Bavendam T, Norton J, Kirkali Z, et al. Advancing a Comprehensive Approach to the Study of Lower Urinary Tract Symptoms. *J Urology* 2016; Vol 196:1342. doi.org/10.1016/j.juro.2016.05.117

Meeting Objectives

Tamara Bavendam, M.D., M.S., Senior Advisor of Women's Urologic Health, KUH, NIDDK, NIH

Dr. Tamara Bavendam thanked the organizing committee, which included representatives from across the NIH and urology professional societies, and acknowledged the speakers, including faculty members who contributed to planning the meeting. Dr. Bavendam reflected on the path to increasing R01 applications for benign urology research within the NIDDK that may have begun with the March 2014 NIDDK Summit on Urinary Incontinence Clinical Research in Women. The outcome from the 2014 summit revealed that treatments were effective; however, the best responders (the populations that responded best) were not well defined. In 2015, the NIDDK convened three other meetings—the Workshop on Behavioral and Psychosocial Factors in Women with Urinary Incontinence, the Research Needs for Effective Transition in Lifelong Care of Congenital Genitourinary Conditions meeting, and the Urinology Think Tank—which have set the framework for the 2017 and 2018 Workshops on Individualizing Treatment for Urinary Incontinence.

The objectives of today's meeting are to enhance interdisciplinary thinking, inform participants of novel research methodologies, guide interdisciplinary teams in the development of actionable research plans, and provide time for research teams to confer with experts in clinical trial methodology and biostatistical methods. The agenda consists of four topical sessions related to evolving research questions into research plans, a session dedicated to elevator pitches, and a poster session. Each topical session will include three to four individual presentations, followed by a moderated discussion that allows audience participation. After the main scientific session, participants will assemble into groups for the team-based research planning session/activity.

The March 2017 workshop, which focused on broadening the framework for individualizing treatment for UI, focused on an underlying problem: UI treatments are not effective in all patients with the same urologic condition (e.g., type of UI). Developing better treatments seems to be the most logical approach, but this would be a long-term solution. Targeting the current effective treatments (e.g., behavioral, neuromodulation, pharmacological, surgery) to determine the best candidate for each treatment is a solution that can be achieved in the near term. In fact, performing broad and in-depth characterizations of

UI patients using novel research strategies across the current treatments could begin to stratify the positive responding patients (responders) from patients not responding (nonresponders). Therefore, current treatments could be targeted to the patients who are most likely to benefit without undue burden/side effects to nonresponders. Nonresponders then would become the focus of novel treatment strategies.

Dr. Bavendam acknowledged the authors of the 2017 meeting report titled "Individualizing Urinary Incontinence Treatment: Research Needs Identified at a National Institute of Diabetes and Digestive and Kidney Diseases Workshop," which was drafted and published in a short amount of time. She called attention to Table 1 of the report, which details the potential modifiers of treatment response stratified by biopsychosocial characteristics of the patient and is a synthesis of the work of the 2017 brainstorming breakout groups and can be a framework for developing research questions for a UI research plan.

As a funding institution, the NIDDK seeks to stimulate investigator-initiated research that addresses the mission of the NIDDK, which includes benign urology. Independent investigators at all career levels are encouraged to submit ideas about which they are passionate, and the NIDDK will facilitate building interdisciplinary research collaborations to support development and ongoing involvement of clinician scientists in benign urology research. As investigators continue supporting research centers by developing sustainable and scalable projects, their work will ensure a favorable payline for the NIDDK, which will attract top researchers.

To date, urology research in the KUH has been supported primarily through the U01 funding mechanism—the percentage of R01-supported research has been increasing and is expected to continue. The NIDDK is heavily invested in investigator-initiated research (R01s) and uses training grants (T32s) and research network Requests for Applications (RFAs) to support the R01 research pool. Training grants have been an ongoing path to successful R01s, whereas research networks have been less effective than desired. Because clinical trials are mostly supported by RFAs and increasing the R01 pool would affect future investments, alternative mechanisms for funding such trials is essential. Options include conducting studies at multiple centers. For studies planned at one or two centers, the R01 mechanism will be applicable; the NIDDK currently is soliciting applications for investigator-initiated trials via the PA-18-330 R01. For studies planned at three or more centers, applications will be solicited via the PAR-18-423 U34 and PAR-18-415 U01.

Dr. Bavendam encouraged interested applicants to email a 1- to 2-page draft of the research concept to one or more program officers at NIH Institutes and Centers (ICs) that fund UI research (e.g., NIDDK, National Institute of Nursing Research, National Institute of Biomedical Imaging and Bioengineering) prior to submitting an R01 application. She highlighted the NIH All of Us Research Program, a key initiative that is poised to be a conduit to advance the importance of benign urologic conditions across the NIH. The opportunity exists for urology researchers to submit Use Cases, comment on existing cases, and rate those already submitted. A detailed handout has been included in the meeting materials.

References

1. Norton JM, Bradley CM, Brady SS, et al. Individualizing Urinary Incontinence Treatment: Research Needs Identified at a National Institute of Diabetes and Digestive and Kidney Diseases Workshop. *J Urology* 2017; Vol 198:1179. doi.org/10.1016/j.juro.2017.11.118
2. All of Us Research Program. allofus.nih.gov.

Session I: Novel Research Methodologies—Database Analysis

Moderator: Rahel Nardos, M.D., Assistant Professor, Urogynecology/Obstetrics and Gynecology, Oregon Health & Science University, School of Medicine

Dr. Rahel Nardos pointed out the challenge of targeting UI therapies to individual patients due to the limited understanding of the risk factors that contribute to a patient's pathophysiology. This has made it difficult for clinicians to counsel patients on treatment outcomes and risk. The ideal scenario would be to recommend the best therapy for a urology patient based on the patient's response to a few key questions that were derived from targeted approaches, models, or predictors. Dr. Nardos remarked on the motivation for this session, which is to embrace the use of the expertise of scientists from urology and other disciplines (e.g., neuroscientists, computational scientists) to help interpret data for answering key questions about predicting therapies.

Risk Prediction Models for Urinary Incontinence and Pelvic Floor Disorders (PFDs)

Matthew Barber, M.D., M.H.S., Professor and Chair, Obstetrics and Gynecology, Duke University

Dr. Matthew Barber discussed the advantages of risk prediction models for providing care for UI and PFD patients and shared examples of validated UI and PFD prediction models developed from existing data sets. He acknowledged the many collaborators, including the PFD Prediction Analytics Team at the Cleveland Clinic, who have helped shape this work. Dr. Barber pointed out that patients often ask clinicians for predictions on whether a proposed treatment would work and offered a case scenario in which two women, 45 years of age, from different race/ethnicity backgrounds, present to the clinic with stress UI (SUI). The assumption is that the clinical characteristics are identical. When the women ask about the chances of being continent (i.e., function restored) after the proposed surgical procedure, the clinician has several sources to help in making a prediction (e.g., use of prior knowledge, experience or data on the overall average success rate for all patients). Yet, most of these options, except for applying a model, are based on clinical judgment, which is prone to errors.

Dr. Barber pointed out that prediction models show consistent superiority over clinical judgement and are less prone to cognitive biases. Crude decision trees often are used to compute risk in clinical decision-making but are not optimal because of the limited number of variables used and the heterogeneity that exists within the risk groups. Increasing amounts of data and computing power allow one to build the most accurate model possible, test the model in a bedside setting as a nomogram or computer application (app), or integrate directly into the electronic medical record. Adopting these simple steps—build, test, integrate—will predict patient outcome more accurately, resulting in improved patient counseling and treatment decisions.

Dr. Barber detailed risk prediction models for UI that he and his collaborators developed. A model for predicting risk of UI and adverse events after surgery in women with SUI was built and internally validated using data from the Urinary Incontinence Treatment Network (UITN) Trial of Mid-Urethral Slings (TOMUS) study. The model was externally validated using three combined data sets, one publicly available data set, and clinical trial data from two studies conducted at the Cleveland Clinic. These model data sets were converted into an online calculator and tested on the case scenario previously described. Results showed that in both women treated with a retropubic sling, the risk of any adverse event was similar, but one of the women had a greater risk of a bothersome urgency UI (UUI) outcome. Modeling the high-risk UUI patient after a different procedure, treatment with a transobturator sling, showed a similar UUI outcome, but the risk of any adverse event was significantly reduced. This model provides an individualized assessment of the comparative effectiveness of available treatment options that would be useful for patient counseling.

Dr. Barber emphasized that the method for building a predictive model differs from the common statistical methodology; the focus is on predictive accuracy, not causal inference analyses. In addition, supervised machine learning and predictors, including clinical characteristics test results, biomarkers or genomics, can be used for the UI and PFD models. Furthermore, selecting candidate predictors and performing internal and external validations that include clinically acceptable concordance statistic values and predictive probability calibration curves are involved in model development. Other PFD prediction models highlighted include (1) UI and fecal incontinence 6 months after pregnancy; (2) *de novo* SUI after prolapse surgery; (3) recurrence and complications 1 year after prolapse surgery; and (4) PFDs 12 to 20 years after delivery. In general, data inputs primarily included large-scale clinical trials and, to a lesser extent, electronic health records and individual experts. Dr. Barber touched briefly on the use of the model on PFDs 12 to 20 years after delivery to identify high-risk populations, efforts to counsel high-risk patients, and targeting of high-risk patients for PFD prevention.

Dr. Barber informed participants that the predictive models are publicly available on the Cleveland Clinic website: www.rcalc.ccf.org. He concluded that well-constructed statistical models provide more accurate, individualized predictions; patient outcomes predicted more accurately should lead to improved patient counseling and treatment decisions; and prediction models are increasingly possible due to the emergence of advanced analytic techniques, as well as big data (i.e., large data sets) and publicly available data sets.

References

1. Jelovsek EJ, Chagin K, Brubaker L, et al. A Model for Predicting the Risk of *de Novo* Stress Urinary Incontinence in Women Undergoing Pelvic Organ Prolapse Surgery. *Obstet Gynecol* 2014; Vol 129:279–287.
2. Jelovsek JE, Hill AJ, Chagin KM, Kattan MW, Barber MD. Predicting Risk of Urinary Incontinence and Adverse Events after Midurethral Sling Surgery in Women. *Obstet Gynecol* 2016; Vol 127(2):330–340. doi.org/10.1097/AOG.0000000000001269
3. Jelovsek, JE et al. Predicting Risk of Pelvic Floor Disorders 12 and 20 Years after Delivery. *Am J Obstet Gynecol* 2018; Vol 218(2):222e1–222e19. doi.org/10.1016/j.ajog.2017.10.014

Predictive Modeling in Neuroimaging: What Can We Apply to Research on Benign Urologic Conditions?

Damien Fair, Ph.D., Principal Investigator, Oregon Health & Science University, School of Medicine

Dr. Damien Fair described the aspects of neuroimaging predictive modeling that potentially could be used in benign urologic research. Foundational to neuroimaging is functional magnetic resonance imaging (fMRI). Baseline measurements involve selective averaging of a task-related activity, such as eye movement (i.e., open or closed eyes). Many in the field transitioned from using traditional fMRI to using resting-state functional connectivity MRI (fcMRI) after seminal studies revealed functional brain activity that was independent of a task-related activity. Dr. Fair was intrigued by the 2006 fcMRI study that showed distinct regions of the brain that simultaneously activate and were connected in a network. These distinct task-controlled networks were characterized further by applying graph theory to fcMRI. Graph theoretical analyses enable computational scientists to investigate a network, which mathematically is considered to be a collection of points or nodes. For example, networks on the Internet, committees and subcommittees of the U.S. House of Representatives, U.S. driver commuting patterns, and the yeast interactome are dynamic systems that can be characterized using graph theory. Patterns of systems such as these are quantified using metrics related to the network's structure.

Recent brain imaging research being conducted in the urology community shows that resting-state fcMRI and graph theory analysis of brain activity of patients with urological conditions (e.g., overactive bladder disorder [OAB], UUI) showed similarities to the activity of established task-controlled brain networks,

cingulo-opercular/salience network, and the default network. These findings stimulated further investigations by Drs. Fair and Nardos and other colleagues on whether distinct brain regions could predict the presence and severity of UUI in patients. Their results showed similarity in the regions of the brain related to UI and the cingulo-opercular/salience and default networks. A recent PubMed search revealed that more than 4,500 studies investigating the default network and more than 2,000 cingulo-opercular/salience network studies related to mental health disorders have been performed since 2006. Dr. Fair summarized that both task fMRI and resting-state fcMRI have shown promising CNS relationships in UUI and OAB patients. Many of the brain regions identified are important for generalized control processing in many mental health and other brain disorders. When or if the brain becomes a therapeutic target for urological research, vast amounts of studies involving the treatment of a variety of disorders in the literature on these systems are available to be built upon.

Dr. Fair next described the heterogeneity problem in mental health from a neuroscientist's perspective and pointed out the importance of characterizing this heterogeneity. Despite the increased knowledge of the brain's connected networks and generalized control processing, progress in mental health has been impeded by the heterogeneity that exists within many clinical populations. He emphasized that the goal in studying complex behaviors, symptoms, and brain physiology is to directly associate these data with patients' near- or long-term clinical trajectories or health issues.

Neuroscientists are not clear on whether the information from noninvasive tools assists in predicting future outcomes or whether this information can help to tailor management or provide targets for early interventions and therapeutics to improve health outcomes. In general, the statistical mean model is used more often to evaluate the differences between groups. This model assumes that the diagnostic categories being used represent etiologically homogenous groups and that the control population represents one homogenous group. Many existing theories suggest a heterogeneity problem, and it has been proposed conceptually that distinct subgroups exist within various clinical disorders. Yet, it is challenging to demonstrate empirically that such subgroups exist because of the computational complexity that increases with sample size. Several methods are available to address this challenge, including graph theory and community detection, which has seen both successes and failures.

Dr. Fair remarked on an underlying problem that ensues when the data being generated are not important to the questions being asked. If ideas regarding heterogeneity are accurate, then different clusters or distributions are likely to result, depending on the question or outcome of interest. One way Dr. Fair's neuroimaging laboratory is addressing this issue is by using machine learning, decision trees, and random forest algorithms combined with graph theory and community detection. Dr. Fair referred participants to recently published data for further details on how this model is being used to study autism; the data are publicly available for downloading.

Dr. Fair briefly demonstrated the use of the functional random forest method to assess OAB, which calculates such outcomes as the OAB questionnaire of health-related quality of life (OAB-Q-HRQL) based on input features that include age, comorbidities, and bladder diary. Preliminary data showed good correlation between predicted values and observed values, heterogeneous OAB cases that were grouped into two subgroups based on OAB-Q-HRQL, slight differences in the distribution of OAB cases across comorbidity subgroups, and similar bladder diaries. Dr. Fair noted that these experiments are ongoing. He speculated that characterization of the heterogeneity in community and clinical populations will need further refinement.

References

1. Biswal B, et al. Functional Connectivity in the Motor Cortex of Resting Human Brain Using Echo-Planar MRI. *Magn Reson Med* 1995; Vol 34(4):537–541.

2. Dosenbach NU, Visscher KM, Palmer ED, et al. A Core System for the Implementation of Task Sets. *Neuron* 2006*;* Vol 50(5):799–812. doi.org/10.1016/j.neuron.2006.04.031
3. Fair DA, Bathula D, Nikolas MA, Nigg JT. Distinct Neuropsychological Subgroups in Typically Developing Youth Inform Heterogeneity in Children with ADHD. *Proc Natl Acad Sci* 2012; Vol 109(17):6769–6774. doi.org/10.1073/pnas.1115365109
4. Nardos R et al. Abnormal Functional Connectivity in Women with Urgency Urinary Incontinence: Can We Predict Disease Presence and Severity in Individual Women Using Rs-fcMRI. *Neurourol Urodyn* 2016; Vol 35(5):564–573. doi.org/10.1002/nau.22767
5. Feczko E, et al. Subtyping Cognitive Profiles in Autism Spectrum Disorder Using a Functional Random Forest Algorithm. *Neuroimage* 2017; Vol 172:674–688. doi: 10.1016/j.neuroimage.2017.12.044

Moderated Discussion and Audience Questions and Answers

Dr. Nardos asked about the challenges of having adequate and relevant data for developing predictive models to answer research questions. Dr. Barber agreed that challenges exist and that model development is dependent upon the available data. Population-based data sets are becoming increasingly more available and can be linked into a single data set. The challenge in data analytics is that many of the large cohort studies are not capturing data on bladder outcomes. One primary goal should be to ensure that these data are included in large-scale initiatives, such as the All of Us Research Program.

Dr. Sonya Brady wondered whether it would be accurate to characterize the predictive models as machine driven, rather than hypothesis driven, and whether testing for two-way and three-way interactions is being considered. Dr. Barber explained that the risk prediction models use supervised machine learning and traditional techniques. The hypothesis being tested is whether predictions can be made using the candidate predictors (effector-based model). Dr. Fair added that the unsupervised machine learning approaches used in his laboratory were less successful in clinical samples. The goal in any predictive modeling is to identify the best model rather than focusing on an individual hypothesis.

Dr. Margot Damaser observed that the risk-based and neuroimaging predictive models are associative in nature and provide limited information on mechanisms that are of primary interest to basic research scientists. Dr. Fair explained that the neuroimaging predictive models are not designed to answer clinical questions but are built to identify mechanisms or targets related to a given outcome for an individual patient. Dr. Barber added that predictive models, in general, aim for the best results and that confounders can be used to inform the models.

Dr. Laura Lamb asked whether the predictive models favored biological parameters over patient-reported outcomes (PRO). Dr. Fair noted that in his experience using biological parameters to build predictive models, the results have been inconsistent. Dr. Lamb also wondered whether a modeler's confidence in a predictive model depends on the number of variables used to build the model. Dr. Barber explained that models aim for the best accuracy, which may be achievable with fewer variables. Dr. Fair agreed that the goal when building a model is to achieve the simplest design that has the best accuracy.

Dr. Star observed that unsupervised clustering often yields inconsistent predictions and wondered what predictive modelers and data analytics experts have experienced. Dr. Fair acknowledged that unsupervised clustering of groups is problematic and noted his laboratory's somewhat successful but limited experience in working with unsupervised processing of clinical data. Unsupervised models tend to make predictions that are not important to the question being asked because the population clustering options are too numerous.

Dr. Elizabeth Mueller pointed out that the urological predictive models are basing their predictions on symptoms that are vague compared to cardiovascular disease models that use concrete data. Dr. Fair commented that it is the symptoms that are being treated or modeled; use of other variables would depend on the goals for the model. The models are not intended to reveal the cause of the symptoms.

Session II: Novel Research Methodologies—Trial Designs

Moderator: William Stuart Reynolds, M.D., M.P.H, Vanderbilt University

Applying Master Methodologies to Enhance Trial Designs

Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration (FDA)

Dr. Janet Woodcock discussed new clinical trial designs for medical product development, noting that such trials typically yield only a small pay-off despite significant investment. Factors that warrant novel trial designs include heterogeneity in patients or stages of disease, as well as interventions that change the number of eligible candidates. In general, a clinical trial life cycle in an academic setting begins with obtaining funding through a granting mechanism/system in which principal investigators and collaborators submit a proposal to a funding agency, a process that could take 1 year or longer to complete. Additional months are necessary for protocol development and finalization, setup of study personnel, establishment of databases, and addressing of any other infrastructure needs. The study is then conducted, although it often does not achieve full patient enrollment. After an active duration, the study close-out procedures, such as data analysis and dissemination of findings or conclusions via publications, require additional time investment. Dr. Woodcock remarked that academic trials often are designed to answer a single key question and may need additional studies to be conclusive. Even after a lengthy clinical trial, questions remain about ways to advance the field and translate evidence for decision-making regarding patient treatment.

Dr. Woodcock pointed out that the industry version of a clinical trial life cycle tends to be more efficient due to the initial costs and investments by the sponsor and heavy reliance on the success of the trial for future growth. Development of the protocol, investigator brochures, and informed consent procedures are first in the cycle and can take several months to complete. Next steps include negotiating with clinical sites regarding cost and timelines, developing case report forms and a monitoring plan, submitting a final protocol to regulatory agencies, and training selected clinical sites. The study is conducted, followed by the close-out processes to lock databases, perform data cleanup, write study reports, and disseminate study findings via publications. The total time invested can span multiple years and yield an answer to only a single research question. Although more organized, the industry method for conducting trials does not result in rapid learning, and the clinical-related cost of medical product development is unsustainable. Many studies do not build upon generalizable knowledge, which discourages new clinical researchers from entering the field.

Dr. Woodcock described three innovative methods that may help alleviate the challenges of conducting clinical trials: (1) master protocols, (2) pragmatic trials using digital health record data, and (3) real-world evidence (RWE). Master protocols overarchingly address a disease or condition in a continuous and ongoing manner and generally use a common infrastructure (e.g., data capture, governance, personnel), resulting in major cost savings. Adaptive designs can be used depending on the questions being addressed, and multiple substudies can start and stop under the master protocol, thereby circumventing the delays identified in typical trial designs. In addition, master protocols are more efficient in answering questions, useful for addressing comparative outcome questions, and used for precision medicine, but they require more work in advance to set up the study. Examples of master protocols include a study of a

disease in multiple subgroups or efforts to screen various interventions for further study, such as the Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2 (I-SPY 2) study.

Pragmatic trials using digital health record data are supported in the NIH Health Care Systems Research Collaboratory. Making interventions and assessments compatible with the clinical workflow by collaborating closely with health care personnel is key. Randomization and informed consent can be included initially and subsequently followed up by the digital health record. RWE, information derived from real-world data (e.g., health records or claims data), is a promising approach to collect data on exploratory or off-label use of a drug outside of a clinical trial.

Dr. Woodcock highlighted other trial design issues being addressed by the FDA, including ways to improve the availability of extant trial data. She emphasized that the questions to be answered in a study drive the choice of trial design. Dr. Woodcock summarized the stumbling blocks associated with a typical trial design: It constrains the number of interventions that can be tested or the number of clinical questions that can be answered due to the amount of time and resources needed, impedes the movement of new scientific knowledge into real advances for patients, increases the cost of medical product development, and closes the clinical communities of practice out of clinical research. The use of new trial methodologies—master protocols, pragmatic trials, or RWE—aim to ameliorate some of these issues; the next few years should reveal the impact of such designs. The FDA will continue to need academic participation and evaluation of clinical trials.

Reference

1. Woodcock J, LaVange L. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. *NEJM* 2017; Vol 377(26):2509–2512.

Getting SMART about Adaptive Interventions in Benign Urologic Conditions Research
Daniel Almirall, Ph.D., Associate Professor, Survey Research Center, University of Michigan

Dr. Daniel Almirall presented on adaptive interventions for individualizing UI treatment and provided examples. Adaptive intervention, or dynamic treatment regimen, is a prespecified sequence of decision-rules used to guide altering an intervention at critical decision points during education or care. In many areas of health care—particularly in the management of chronic diseases—intervention often involves a sequential, individualized approach in which treatment is adapted and re-adapted over time. He described an example of an adaptive intervention in autism—one of Dr. Almirall's areas of expertise—that could be modeled conceptually for UI. In this example, minimally verbal (i.e., less than 20 words used spontaneously) children, 5 to 8 years of age, with autism spectrum disorder (ASD) were started on a behavioral intervention—Joint-Attention, Structured Play, Enhanced Milieu Teaching (JASP+EMT)—for 12 weeks as stage 1 treatment. After 12 weeks, the responder status was assessed and evaluated. Study participants were considered responders if a 25 percent or greater change on seven measures of language acquisition was observed. After status assessment, children identified as responders continued the stage 1 treatment without change for an additional 12 weeks, whereas children identified as slow responders received an augmented treatment, JASP+EMT plus a speech-generating device (e.g., Augmented and Alternative Communication [ACC]), for an additional 12 weeks.

Dr. Almirall next led the participants through an exercise to develop a hypothetical adaptive intervention for UI from a clinical perspective. Possible treatment components might include preventive behavioral interventions, prescription medications, physical therapy, or engagement/adherence interventions. Decisions on packaging treatment components into an optimal individually-tailored, adaptive intervention designed to answer critical scientific questions would need to be addressed. Costs, burden to patients,

adherence, and patient monitoring all are factors to consider for the individual components. In reality, studies can be designed to address these issues.

Dr. Almirall elaborated on three types of directions scientists might consider for adaptive intervention research. He used the multiphase optimization strategy (MOST), a framework for guiding how one could develop a program of research that leads to an optimized intervention, which includes the following types of strategies: (1) prepare or address feasibility/acceptability considerations concerning the components of an adaptive intervention; (2) build or optimize an adaptive intervention; or (3) evaluate an adaptive intervention. Type 1 research questions could involve preparing for an adaptive intervention by assessing feasibility via a pilot study (e.g., whether it is possible to identify responders vs. non-responders in actual practice settings) or using observational studies to gather preliminary data (e.g., identifying the typical rate of non-response). Type 2 research questions might focus on building or optimizing an intervention (e.g., how two intervention components work together in sequence or the best tailoring of variables and decision rules to optimize outcomes) using an enhanced non-responder trial or a more novel design. Type 3 research questions could consider evaluating an adaptive intervention by conducting a standard randomized control trial (RCT) or a noninferiority trial, for example.

An optimization tool now popular for Type 2 research questions is the Sequential, Multiple Assignment, Randomized Trial **(**SMART), a multistage randomized trial design developed specifically for building a high-quality adaptive intervention. A SMART is not an alternative or competitor to the RCT, which is used for evaluation. At each stage of a SMART, subjects are randomized to a set of feasible and ethical treatment options, and treatment options at later stages may be restricted by response to earlier treatments. For example, in a prototypical SMART design, subjects are randomized to one of two treatments and assessed after a preset period or stage 1; responders continue the initial treatment, and slow responders are rerandomized to new treatments in stage 2.

Dr. Almirall presented an autism case study that builds on the example he discussed earlier in his presentation. A first-ever case study of a SMART in autism research, titled "Charactering Cognition in Nonverbal Individuals with ASD," was conducted in collaboration with Dr. Connie Kasari (University of California at Los Angeles [UCLA]) of the UCLA Center for Autism Research and Treatment and Autism Speaks. The population consisted of 61 children with ASD ranging from 5 to 8 years of age who were minimally verbal, had a history of a prior intervention, and could function as a child of 2 years of age or older. Intervention components include (1) stage 1 treatment options (JASP or JASP+ACC); (2) the identification of responders and slow responders to stage 1 treatments; and (3) stage 2 treatment options (continue JASP, augment with ACC, or intensify JASP). The 61 participants enrolled in the study were randomized to stage 1 treatment, responders and slow responders to stage 1 treatment were identified, participants were rerandomized to stage 2 treatment, and outcomes were assessed the end of the 24 weeks. Dr. Almirall emphasized that this SMART had three two-stage adaptive interventions embedded within it by design. He pointed out how this example autism SMART was used to compare longitudinal outcomes between three embedded adaptive interventions, which resulted in a 2016 "top 20" autism publication. The study showed that early use of the ACC intervention significantly improved speech after 12 weeks compared to delayed ACC intervention as measured by total spontaneous communicator utterances.

References

1. Collins LM, Baker TB, Mermelstein RJ, et al. The Multiphase Optimization Strategy for Engineering Effective Tobacco Use Interventions. *Ann Behav Med* 2011; Vol 41(2):208–226. doi: 10.1007/s12160-010-9253-x
2. Murphy SA. An Experimental Design for the Development of Adaptive Treatment Strategies. *Statistics in Medicine* 2005; Vol 24(10):1455–1481. doi: 10.1002/sim.2022

3. Almirall D, DiStefano C, Shire L, Chang YC, et al. Longitudinal Effects of Adaptive Interventions with Speech-Generating Devices in Minimally Verbal Children with ASD. *J Clin Child Adolesc Psychol* 2016; Vol 45(4):442.

Moderated Discussion and Audience Questions and Answers

Dr. Jonathan Beckel observed a disproportionate placebo effect in intervention-based clinical trials and asked whether the adaptive intervention design would help to resolve this issue. Dr. Woodcock explained that the objective is first to determine what constitutes a placebo effect in the intervention being tested. Factors could include an exaggeration of symptoms, a threshold of event criteria, small treatment effects, or disease waxing and waning. Including run periods followed by randomizations or conducting pilot studies to determine the placebo effects are some strategies that could help resolve the placebo effect issue. Certain disease states are subject to large placebo effects regardless of the drug being tested.

Dr. Leslee Subak asked about the use of demographics, patient characteristics, or participant preferences in a randomization scheme. Dr. Almirall responded that preference for a treatment could be used to make treatment decisions, and that this could be examined empirically. Dr. Woodcock added that these characteristics or preferences could be addressed in a master protocol as well.

Dr. Theodore Johnson commented on the geriatrics clinical trials in which nine to 10 smaller and less intense interventions are combined and asked whether these could be conducted in a SMART. Dr. Almirall explained that combining or grouping interventions would fit more with optimization rather than with evaluation and suggested that a screening experiment could be appropriate in this case. Embedding a very high number of intervention components into a single SMART is challenging, but doable. Dr. Woodcock added that mathematical modeling is another approach to consider.

Dr. Star pointed out that the SMART appears to work well in experiments that study treatments with a short time to outcome, which often is not the case for renal-related conditions. He asked about the types of UI that would most benefit from a SMART. Dr. Almirall agreed that this is an important and difficult issue. He called attention to the efforts of prevention scientists to investigate child development and cognitive disorders in high-risk populations that might provide more insight into studies that have distal outcomes. In these areas of research, there is a great deal of emphasis on what proximal outcomes to focus on.

Session III: Identifying and Working with Collaborators

Moderator: Linda Brubaker, M.D., Professor, Reproductive Medicine, University of California, San Diego

Dr. Linda Brubaker remarked on the importance of identifying and working effectively with collaborators to accomplish research goals. She explained that speakers from diverse, non-urologic/urogynecologic disciplines will describe their backgrounds, how they became interested in benign urologic conditions research, what their respective field could do to advance research on individualizing treatment for UI, and strategies to engage colleagues in their field.

Engaging Psychometricians in Benign Urologic Conditions Research
Kathryn Flynn, Ph.D., Associate Professor, Department of Medicine, Medical College of Wisconsin

Dr. Kathryn Flynn detailed her path to research on benign urologic conditions. Although her background is in sociology and population sciences, her work as a Ph.D. non-clinician at the Medical College of Wisconsin, a free-standing medical school, put her in close contact with psychometricians. Dr. Flynn's

efforts have focused primarily on patient decision-making, as well as measurement and analysis of patient reported outcomes (PRO), including assisting to develop the Patient-Reported Outcomes Measurement Information System (PROMIS®) Sexual Function and Satisfaction measure and the Symptoms of Lower Urinary Tract Dysfunction Research Network's (LURN's) Comprehensive Assessment of Self-Reported Urinary Symptoms (CASUS). In general, the measurement development process involves the use of mixed methods, qualitative work (e.g., interviews with clinical experts and patients), new-item writing that is understandable and appropriate, translatability review, a recall period, and a statistical analysis to select final items. Dr. Flynn pointed out the challenges in measurement and why it would be best to engage psychometricians to address these challenges. She encouraged participants to become acquainted with measurement experts in their regions so that confidence in an approach is solidified. The best way to engage a psychometrician as a collaborator is to understand what aspect of measurement analysis the research requires. Opportunities to develop a methodically novel concept may be of particular interest to a psychometrician.

Engaging Behavioral Scientists and Public Health Practitioners in Benign Urologic Conditions Research
Sonya Brady, Ph.D., Associate Professor, Epidemiology and Community Health, University of Minnesota

Dr. Brady was trained in clinical psychology and health psychology and is an associate professor at the University of Minnesota School of Public Health. Her research roles align with three distinct and overlapping professional domains, including work as a prevention scientist to identify and intervene on health risk and protective factors through primary and secondary prevention interventions, as a behavioral scientist to understand and shape behavior, and as a social scientist to understand and shape social and ecological determinants of health. Dr. Brady's path to conducting research on benign urologic conditions has been through the NIDDK-supported Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium and the PLUS Scientific and Data Coordinating Center (SDCC) at the University of Minnesota. Working with PLUS SDCC and PLUS investigators has provided Dr. Brady an opportunity to apply her expertise in a manner that is novel to the PLUS and benign urologic conditions domains.

Dr. Brady pointed out that prevention, behavioral, and social scientists can contribute to the individualization of UI in two areas: conceptualization and methods. She discussed ways to engage and interest behavioral scientists and detailed points to highlight when pitching an idea to potential collaborators, including understanding the value one's skill set would bring to interdisciplinary or transdisciplinary science. Developing a working conceptual model of a research question to engage researchers from different disciplines and identifying cross-cutting interests would be helpful. Dr. Brady emphasized that individualizing UI treatment effectively requires understanding the individual in context.

Engaging Primary Care Providers in Benign Urologic Conditions Research
Michelle Seelig, M.D., M.H.S., Physician, Family Medicine, Kaiser Permenente

Dr. Michelle Seelig described herself as an expert generalist who is a trained health services researcher supporting efforts at the Kaiser Permanente Washington Health Research Institute (formerly the Group Health Research Institute) and who practices as a family medicine physician at Washington Permanente Family Health Center. Dr. Seelig became interested in benign urologic conditions research after meeting and later working with Dr. Bavendam on a project that explored the role of physical therapy as treatment for women with chronic pelvic pain (CPP) and bladder dysfunction. The study design was a qualitative analysis of audiotaped face-to-face semi-structured interviews with women in the University of Washington Medical Center health system. Results showed that CPP negatively affects quality of life (QoL). Physical therapy was viewed by patients as a helpful component to treatment, and dealing with the impact of chronic pelvic pain comprised a critical component of the healing process. Drs. Bavendam and

Seelig later developed a pictorial map of the various components (e.g., coping, medications) to illustrate the complicated healing process involved in CPP.

To address how family physicians could contribute to individualizing UI, Dr. Seelig explained how a patient's story provided information on UI that came as a byproduct of the Family Health Center's follow-ups and patient reporting on medications to treat other underlying conditions. Information on UI, in general, is collected during patient wellness visits and is scanned into the medical charts. This would be a sample to consider investigating. Also, two techniques used by family medicine physicians, motivational interviewing and shared decision making, could be modeled for UI. Dr. Seelig called attention to the Chronic Illness Care Model developed by Dr. Edward H. Wagner in collaboration with the then-Group Health Research Institute and the MacColl Center for Healthcare Innovation, which has been widely disseminated and is a framework for health services research.

Engaging Physical Therapists in Benign Urologic Conditions Research
Meryl Alappattu, Ph.D., D.P.T., Research Assistant Professor, Department of Physical Therapy, University of Florida

Dr. Meryl Alappattu, a licensed physical therapist (PT), is trained in rehabilitation science and pain research. PTs, including those specializing in movement related to the pelvis and the pelvic floor muscle (e.g., Kegel exercises), view the body holistically. For example, they might assess how a PFD affects a person's movement in daily living. Dr. Alappattu's start in benign urologic diseases research began during her PT residency in cancer rehabilitation, which involved assisting patients experiencing UI or pelvic pain following cancer therapy. She also established valuable collaborations with other PTs, pain researchers, public health researchers, clinical psychologists, and physicians. Dr. Alappattu remarked that pelvic health is an emerging area of PT practice. The types of research questions a PT would ask include such topics as (1) the prevalence of UI in outpatient PT referrals; (2) the existing associations between musculoskeletal pain conditions and UI; and (3) the impact of PT-delivered interventions on UI and UI-related QoL. To address individualizing UI treatment, a PT would need to assess UI's effect on activities of daily living, QoL, sexual function, and musculoskeletal comorbidities to individualize the intervention (e.g., pelvic floor muscle strengthening) to fit the needs and goals of the patient. She detailed the reasons and methods to engage a PT in benign urologic conditions research. Physical therapy is a conservative treatment in which the impact and value extends beyond muscle strength, pad use, and presence of UI. PTs work in a variety of settings and bring a unique perspective on how UI affects a patient's QoL.

Participants interested in collaborating with a PT are encouraged to engage the specialist or subspecialist suited for the research of interest, know the availability of the PT, and consider ways to address financial support for the research collaboration. Communication is key to maintaining interest from PTs as is providing opportunities to participate in multidisciplinary educational sessions and conferences, as well as collaborating on grant and projects.

Engaging Basic Scientists and Engineers in Benign Urologic Conditions Research
Margot Damaser, Ph.D., Professor, Department of Biomedical Engineering and Glickman Urological and Kidney Institute, Cleveland Clinic Lerner College of Medicine

Dr. Damaser, a dual-trained biomedical engineer and basic scientist, began her career benign urology research as a graduate student when she wrote a successful grant to investigate the neural control and biomechanics of the urinary bladder. Dr. Damaser remarked on how the great need for improvements in urology health care, the excitement of the work, successful funding and collaborations, and the multidisciplinary nature of the research all factor into her desire to continue in this field. Her laboratory

currently is focusing on two main programs: regenerative medicine solutions for PFD and devices to improve diagnosis and treatment of UI.

Scientists and engineers should be engaged in benign urology research for several reasons. Scientists have expertise in the basic biology of the disease, which can assist in identifying mechanisms of action of interventions and genetic factors to predict and modify treatment. Much of a scientist's time is spent carrying out preclinical modeling of physiology and pathology and preclinical testing of potential therapeutics. Engineers are problem solvers and "think out of the box." They can develop novel prototype devices for diagnostics and treatment, and they can design individualized therapeutics. The key to engaging scientists and engineers is to ensure that research interests are aligned, clearly define the problem to be solved, and be open to assisting with research funding.

Moderated Discussion and Audience Questions and Answers

A participant commented that terminology can be specific to a particular discipline and asked about strategies to improve communication and avoid misunderstandings between groups. Dr. Flynn suggested defining and redefining terms at each use. Dr. Seelig added that speaking the patient's language and reusing their words has helped in her practice and suggested avoiding the use of abbreviations without first clarifying them.

Dr. Star commented that PubMed is a tool that can be used to identify potential collaborators by searching by topic of interest and geographical location. He encouraged engaging with potential collaborators early and including patients as collaborators in the design phase of a project.

Dr. Michael Kong noted the importance of engaging collaborators who are equally motivated to conduct the research. Dr. Alappattu suggested having conversations about expectations early in the collaboration and establishing rules of engagement. Dr. Brady remarked on the value of conducting information-gathering interviews with a collaborator prior to starting a project.

Session IV: Elevator Pitches

Moderator: Jenna Norton, M.P.H, NIDDK, NIH

Ms. Jenna Norton explained that this session will consist of scientific elevator pitches to potential collaborators. Participants volunteered to present a 2-minute speech explaining what they hope to achieve, whom they would like to engage in their research, and what they need to accomplish their goals.

ELEVATOR PITCH PRESENTERS

Nicole Gilbert, Ph.D.
Obstretrics and Gynecology
Washington University School of Medicine in St. Louis
Scientific Pitch: Bacterial Vaginosis

Michael Kong, Ph.D.
Center for Bioelectrics
Old Dominion University
Scientific Pitch: A Novel Large-Scale Plasma Source

Steve Majerus, Ph.D.
Advanced Platform Technology Center
U.S. Department of Veterans Affairs
Scientific Pitch: Wireless Bladder Pressure Monitor for Closed-Loop Bladder Neuromodulation

Heidi Brown, M.D., M.S.
Obstetrics and Gynecology and Urology
University of Wisconsin–Madison
Scientific Pitch: Potential Reach of Community-Based Continence Promotions

Amy Zhang, Ph.D.
Frances Payne Bolton School of Nursing
Case Western Reserve University
Scientific Pitch: Behavioral Intervention and Mobile App for Managing Urinary Incontinence

Colleen Fitzgerald, M.D.
Obstetrics and Gynecology
Loyola University Medical Center
Scientific Pitch: Pelvic Pain Disorders and Urinary Incontinence

PRESENTED POSTERS

Show Me the Reach: Who Is Left Out to Dry with Community-Based Continence Promotion?
Heidi Brown, M.D.[1]; Tamara LeCaire, Ph.D.[2]; Anna Drewry, M.D.[1]; Paul Peppard, Ph.D.[2]; Kristen Malecki, Ph.D.[2]; F. Javier Nieto, M.D., Ph.D.[2,3]; Jane Mahoney, M.D.[1]
[1]University of Wisconsin–Madison School of Medicine and Public Health; [2]Survey of the Health of Wisconsin; [3]College of Public Health and Human Sciences at Oregon State University

Gardnerella Vaginalis
Nicole Gilbert, Ph.D.[1]
[1]Washington University School of Medicine in St. Louis

Identifying Alternative Mechanisms That Contribute to Urgency Urinary Incontinence
Lisa Karstens, Ph.D.[1]; Mark Asquith, Ph.D.[2]; James T. Rosenbaum, M.D.[2,3]; Shannon McWeeney, Ph.D.[1]; W. Thomas Gregory, M.D.[4], Damien Fair, Ph.D.[5,6]; Rahel Nardos, M.D.[4]
[1]Division of Bioinformatics and Computational Biology, Oregon Health & Science University; [2]Division of Arthritis and Rheumatic Diseases, Oregon Health & Science University; [3]Devers Eye Institute; [4]Division of Urogynecology, Oregon Health & Science University; [5]Department of Psychiatry, Oregon Health & Science University; [6]Department of Behavioral Neuroscience, Oregon Health & Science University

Toward Personalized Medicine and Individualized Diagnosis of Interstitial Cystitis/Bladder Pain Syndrome Using Machine Learning Developed Risk Score
Laura E. Lamb, Ph.D.[1,2]; Joseph J. Janicki[1;] Sarah N. Bartolone, M.S.[1]; Bernadette M.M. Zwaans, Ph.D.[1,2]; Kenneth M. Peters, M.D.[1,2]; Michael B. Chancellor[1,2]
[1]Department of Urology, William Beaumont Hospital, Royal Oak, Michigan; [2]Oakland University William Beaumont School of Medicine, Rochester Hills, Michigan

Murine Voiding Data Collection System
Toy Gee Lee, M.D.; Paula Doyle, M.D.; Ron Wood, Ph.D.
University of Rochester, School of Medicine and Dentistry, Rochester, New York

Ultrasound Imaging for the Monitoring of Cyclophosphamide-Induced Cystitis in the Mouse Model
Toy Gee Lee, M.D.; Paula Doyle, M.D.; Liling Zou, Ph.D.; Dongmei Li, Ph.D.; Robert Schor, Ph.D.; Ron Wood, Ph.D.
University of Rochester, School of Medicine and Dentistry, Rochester, New York

Ultrasound Imaging of Murine Bladder Cystitis
Toy Gee Lee, M.D.; Paula Doyle, M.D.; Ron Wood, Ph.D.
University of Rochester, School of Medicine and Dentistry, Rochester, New York

Therapeutic Exploitation of Ipse, a Urogenital Parasite-Derived Host Modulatory Protein, for Chemotherapy-Induced Hemorrhagic Cystitis
Evaristus C. Mbanefo[1,2]; Loc Le[1]; Luke F. Pennington[3]; Justin I. Odegaard[4]; Theodore S. Jardetzky[3]; Abdulaziz Alouffi[5]; Franco H. Falcone[6]; Michael H. Hsieh[1,2,7]
[1]*Bladder Immunology Group, Biomedical Research Institute, Rockville, Maryland;* [2]*Division of Urology, Children's National Medical Center, Washington, DC;* [3]*Department of Structural Biology, Stanford University School of Medicine, Stanford, California;* [4]*OneOme, Redwood City, California;* [5]*Life Science and Environment Sector, King Abdulaziz City for Science and Technology, Riyadh, Saudi Arabia;* [6]*Division of Molecular Therapeutics and Formulation, School of Pharmacy, University of Nottingham, Nottingham, United Kingdom;* [7]*Department of Urology, The George Washington University, Washington, DC*

Bladder Wall Micromotion Measured with M-Mode Ultrasound During Urodynamics in an Anesthetized Pig Model and Women with Overactive Bladder
Anna S. Nagle, Ph.D.[1]; Zachary E. Cullingsworth[1]; Uzoma A. Anele, M.D.[2]; Charles R. Blocher, M.S.[2]; Adam P. Klausner, M.D.[2]; John E. Speich, Ph.D.[1]
[1]*Department of Mechanical and Nuclear Engineering, Virginia Commonwealth University School of Engineering, Richmond, Virginia;* [2]*Department of Surgery, Virginia Commonwealth University School of Medicine, Richmond, Virginia*

Effects of Patient-Centered Interventions on Persistent Urinary Incontinence after Prostate Cancer Treatment
Amy Zhang, Ph.D.
Case Western Reserve University, Cleveland, Ohio

From a Patient Perspective: Is a Behavioral Intervention to Urinary Incontinence Worthy of Trying?
Amy Zhang, Ph.D.
Case Western Reserve University, Cleveland, Ohio

Usage and Results of a Mobile App for Managing Urinary Incontinence
Amy Zhang, Ph.D.[1]; Jeff Pepper[2]
[1]*Case Western Reserve University, Cleveland, Ohio;* [2]*President and CEO, Touchtown Inc., Oakmont, Pennsylvania*

Individualized Treatment via Specifying Origins of the Dysfunction of the EAS/EUS in Aging
Yingchun Zhang, Ph.D.
University of Houston, Houston, Texas

Session V: Translational Pathway for Individualized Therapies

Moderator: Margo Damaser, Ph.D., Professor, Department of Biomedical Engineering and Glickman Urological and Kidney Institute, Cleveland Clinic, Lerner College of Medicine at Case Western Reserve University and Senior Research Career Scientist, Louis Stokes Cleveland VA Medical Center, Cleveland, OH

Bench-to-Bedside Models in Cardiovascular Precision Medicine Research

W. H. Wilson Tang, M.D., Professor, Cleveland Clinic Lerner College of Medicine

Dr. W. H. Wilson Tang pointed out that the current standard of care for heart failure is based on a generalizable set of recommendations that outlines a common treatment for all patients. This nontargeted approach does not stratify patients according to risk or response to treatment, yet therapies have been effective. The standard treatments have improved quality of life, decreased hospitalizations, and improved hemodynamics; however, patients must manage six or seven prescriptions. Another approach to treatment, precision cardiovascular medicine, has the potential to provide new medical knowledge for the cardiology community that could be translated into clinical practice. For example, precision cardiology involves disease phenotyping, data generation, and data collection, including use of omics and clinical data sets. Data integration encompasses machine learning to deliver data-driven disease subtyping and patient stratification. Dr. Tang called attention to one of the first National Heart, Lung, and Blood Institute precision medicine initiatives, the Pulmonary Vascular Disease Phenomics (PVDOMICS**)** study, which aims to perform comprehensive phenotyping and endophenotyping across the World Health Organization classifications for pulmonary hypertension. The goal is to deconstruct the traditional classifications and define new meaningful subclassifications for patients with pulmonary vascular disease.

Dr. Tang remarked that the challenges in cardiovascular precision medicine are that the disease pathogenesis is complex, nurture is greater than nature, and the associations do not equate to causation and can distract from or compete with ongoing public health efforts and resource allocations. He reported on four bench-to-bedside approaches or models used in cardiovascular precision medicine research that he has encountered over the past 10 years of clinical research and practice. Dr. Tang emphasized that these cardiology models are the result of highly collaborative and multidisciplinary efforts and reflect applications evolved from the frustration of the current conundrum faced by the cardiology community. He then described four bench-to-bedside approaches in the cardiovascular arena that can be adopted in other specialties.

Redefine Pathophysiologic Understanding through Rare Genetic Diseases to Identify Therapeutic Targets. Dr. Tang reported that mutations in the proprotein convertase subtilisin/kexin type 9 serine protease (*PCSK9*) gene have been linked to familial hyper cholesterolemia in humans. This discovery has justified the strategy of inhibiting *PCSK9* to reduce plasma levels of low-density lipoprotein cholesterol in humans. Within 10 years of discovery, candidate *PCSK9* inhibitors were approved by the FDA. This is a clear example of genomic insights informing drug discovery. In addition, mutations in the sarcomere protein genes lead to hypertrophic cardiomyopathy (HCM), and HCM variants have been shown to increase sarcomeric power and impair relaxation. Furthermore, a small-molecule inhibitor of sarcomere contractility, MYK-461 (Mavacamten), inhibits myosin ATPase and improves HCM biophysical and clinical findings. In fact, Mavacamten currently is in Phase III trials and is one of the first cardiovascular gene-directed therapies tested for inherited cardiac diseases.

Gain Insights into Molecular Signatures to Detect Transplant Rejections. Dr. Tang explained that the endomyocardial biopsy, which has been the gold standard to monitor transplant rejection, bases its prediction solely on histology. Newer methods use molecular signatures to classify or reclassify histological diagnoses. An FDA-approved method utilizing transcriptomic profiles in peripheral blood cells correlated with biopsy results and currently is being used in the clinic. Also, diagnosis of acute rejection can be assessed by measuring circulating cell-free donor-derived DNA in proof-of-concept studies of heart and lung transplant patients and already is available in the kidney transplant arena.

Discover Extra-Cardiac Pathophysiologic Pathways through Genomics and Metabolomics as Novel Therapeutic Targets. Dr. Tang and his laboratory used a metabolomics approach to show that gut microbiota-dependent choline/carnitine metabolism leads to trimethylamine (TMA)/trimethylamine N-oxide (TMAO) production that predicts risk for cardiovascular disease in mice. The researchers also found that certain dietary nutrients possessing a TMA moiety, namely choline/phosphatidylcholine and L-carnitine, participated in the development of atherosclerotic heart disease. In humans, they found that the production of TMAO from dietary phosphatidylcholine was dependent on metabolism by the intestinal microbiota. Increased TMAO levels were associated with an increased risk of incident major adverse cardiovascular events. Employing precision medicine strategies to target TMAO could improve cardiovascular health. New approaches to precision health research, such as personalized nutritional profiling, also could be considered.

Apply Novel Technologies in Microbial Genomics to Better Inform Care. Dr. Tang touched briefly on one model in this category—next-generation sequencing for infectious diseases. Microbial infections have been observed in heart valve surgery, and sequencing is emerging as one method to identify and characterize bacteria in excised heart valves. In the advent of these new technologies, the clinician is, in some ways, obligated to critically evaluate the methods being used to inform care better.

In closing, Dr. Tang pointed out that prerequisites—including safe and assessible diagnostics, learning, health systems, development of affordable targeted therapies, and updated research and regulatory policies—would need to be addressed before any attempts to operationalize precision medicine. He emphasized the necessity of coordinating and creating research practices and of determining ways to implement precision medicine.

References

1. Johnson KW, et al. Enabling Precision Cardiology through Multiscale Biology and Systems Medicine. *JACC: Basic to Translational Science* 2017; Vol 2(3):311–327.
2. Hemnes AR, et al. PVDOMICS: A Multi-Center Study to Improve Understanding of Pulmonary Vascular Disease through Phenomics. *Circ Res* 2017; Vol 121(10):1136–1139. doi: 10.1161/CIRCRESAHA.117.311737
3. Cohen CC, et al. Sequence Variations in PCSK9, Low LDL, and Protection Against Coronary Heart Disease. *N Engl J Med* 2006; Vol 354:1264–1272. doi: 10.1056/NEJMoa054013
4. Teekakirikul P, Padera RF, Seidman JG, Seidman CE. Hypertrophic Cardiomyopathy: Translating Cellular Cross Talk into Therapeutics. *J Cell Biol* 2012; Vol 199(3):417–421. doi: 10.1083/jcb.201207033
5. McNally EM, Barefield, DY, Puckelwartz MJ. Genetic Variation in Cardiomyopathy and Cardiovascular Disorders. *Circ J* 2015; Vol 79(7):1409–1415. doi: 10.1253/circj.CJ-15-0536
6. Alamo L, Ware JS, Pinto A, et al. Effects of Myosin Variants on Interacting-Heads Motif Explain Distinct Hypertrophic and Dilated Cardiomyopathy Phenotypes. *Elife* 2017; Vol 6:e24634. doi: 10.7554/eLife.24634

7. Green EM, et al. A Small-Molecule Inhibitor of Sarcomere Contractility Suppresses Hypertrophic Cardiomyopathy in Mice. *Science* 2016; Vol 351(6273):617–621. doi: 10.1126/science.aad3456
8. Pham MX, Teuteberg JJ, Kfoury AG, et al. Gene-Expression Profiling for Rejection Surveillance after Cardiac Transplantation. *N Engl J Med* 2010; Vol 362(20):1890–1900. doi: 10.1056/NEJMoa0912965
9. De Vlaminck I, Valantine HA, Snyder TM, et al. Circulating Cell-Free DNA Enables Noninvasive Diagnosis of Heart Transplant Rejection. *Sci Transl Med* 2014; Vol 6(241):241ra277. doi: 10.1126/scitranslmed.3007803
10. Wang Z, et al. Gut Flora Metabolism of Phosphatidylcholine Promotes Cardiovascular Disease. *Nature* 2011; Vol 472(7341):57–63. doi: 10.1038/nature09922
11. Tang WH, Hazen SL. The Contributory Role of Gut Microbiota in Cardiovascular Disease. *J Clin Invest* 2014; Vol 124(10):4204–4211. doi: 10.1172/JCI72331
12. Koeth RA, et al. Intestinal Microbiota Metabolism of L-Carnitine, a Nutrient in Red Meat, Promotes Atherosclerosis. *Nat Med* 2013; Vol 19:576. www.nature.com/articles/nm.3145#supplementary-information. doi: 10.1038/nm.3145
13. Lefterova MI, Suarez CJ, Banaei N, Pinsky BA. Next-Generation Sequencing for Infectious Disease Diagnosis and Management: A Report of the Association for Molecular Pathology. *J Mol Diagn* 2015; Vol 17(6):623–634.

Bench-to-Bedside Development of a Treatment for Urinary Incontinence

Michael Chancellor, M.D., Professor, Department of Urology, Beaumont Health System and Oakland University William Beaumont School of Medicine (OUWB)

Dr. Michael Chancellor described the bench-to-bedside development of a muscle-derived stem cell (MDSC) model for the treatment of SUI, noting that he began his career in urology research with his mentors, Dr. Edward McGuire at Michigan University and Dr. Jerry Blaivas at Columbia University, who are the grandfathers of the pubovaginal sling and collagen periurethral injection. Dr. Chancellor had an idea to improve urethral muscle function and recognized that translating a clinical question to the bench requires a method that is simple and safe and can be performed outside the operating room. Regenerative medicine cellular therapy is one such method. Skeletal muscle biopsy and isolation techniques verified MDSC regeneration *in vitro,* which led to the development and validation of preclinical animal models of SUI, culminating in the first clinical trial of autologous MDSC for SUI.

Dr. Chancellor noted that the potential mechanisms of therapeutic benefit would warrant further development of a MDSC model: (1) new muscle formation, (2) augmentation of existing muscle, and (3) secretion of growth factors that promote tissue remodeling. The next steps toward translation are to consider the technology transfer aspects and engage industry partners. The technology was licensed from the University of Pittsburgh, Dr. Chancellor's prior affiliation, to Cook Myosite Inc., (or Cook) for good manufacturing practices production, toxicity studies, and regulatory requirements. After FDA approvals, the first clinical trial was conducted at the University of Toronto led by Dr. Lesley Carr. The second trial, a multi-institutional study, was conducted at Vanderbilt University Medical Center, William Beaumont Hospital, and Sunnybrook Health Science Center. More recently, studies were initiated to focus on individualizing treatment for women with recurrent or persistent SUI after surgery.

Dr. Chancellor concluded that MDSC may be a novel, safe, durable therapy for women with SUI and noted future directions. He encouraged new investigators to pursue translational research and detailed his steps to a commercial product: (1) he started with an idea that was supported initially by modest seed grants, (2) he generated preliminary data for an NIH grant, (3) he conducted urology research experiments and studies, and (4) he built a portfolio of patents that the University of Pittsburgh could license to industry partners, such as Cook. Dr. Chancellor thanked his colleagues at OUWB and Beaumont Hospital, his collaborators, and the NIH for supporting his work.

References

1. Cannon TW et al. A Tissue-Engineered Suburethral Sling in an Animal Model of Stress Urinary Incontinence. *BJU Int* 2005; Vol 96(4):664–669. doi: 10.1111/j.1464-410X.2005.05702.x
2. Chermansky CJ et al. Intraurethral Muscle-Derived Cell Injections Increase Leak Point Pressure in a Rat Model of Intrinsic Sphincter Deficiency. *Urology* 2004; Vol 63(4):780–785. doi: 10.1016/j.urology.2003.10.035
3. Carr LK et al. 1-Year Follow-Up of Autologous Muscle-Derived Stem Cell Injection Pilot Study to Treat Stress Urinary Incontinence. *Int Urogynecol J Pelvic Floor Dysfunct* 2008; Vol 19(6):881–883. doi: 10.1007/s00192-007-0553-z

Prevalent Myths in the Pharmacological Management of Incontinence

Jeremy Heaton, M.D., M.B.A., Vice President, Medical Urology and Nephrology, Astellas Pharmaceuticals

Dr. Jeremy Heaton discussed prevalent myths in the pharmacological management of UI and ways to translate an idea into a viable individual therapeutic that would attract the attention of pharmaceutical companies. Regarding pharmacological management of UI, the urology community would be wise not to believe that the current treatments satisfy all the needs of patients with incontinence, that there is no unmet need in the urology field, or that targeting any one of the three types of UI would relieve all symptoms. In addition, translational researchers should not think that all good ideas are marketable, that a patent is not necessary, that understanding the mechanism of action is all that is needed, or that it is uncomplicated to help patients without a protected concept.

Dr. Heaton pointed out that, unlike oncology therapies, treatments for such QoL diseases as incontinence do not command high prices. A guide for assisting translation—although not a blueprint for successfully marketable research—consists of four points: (1) conceive, (2) protect, (3) refine, and (4) target. Conceiving a treatment consists of many separate elements, including device and pharmaceutical companies. Protection encompasses intellectual property rights for the patent and the people. Refining focuses on using biomarkers, identifying your patient, and understanding the market and whom the study benefits. Targeting involves addressing the patient's unmet need and market access. To achieve a translation by the pharmaceutical industry for a product, a good idea is only the beginning. Other criteria—including scientific proof, a clear view of an application, use of a biomarker, approved indication, market access strategy, and positive net present value—are weighted heavily. Some strategies to improve individual response include choosing a better molecule, ensuring optimal exposure, and using supportive devices.

Implantable Medical Device for Treatment of Urologic Conditions with Onboard Distributed Closed-Loop Research Capability

Lance Zirpel, Ph.D., Chief Scientist, Research and Core Technology, Pelvic Health and Gastric Therapies, Medtronic Restorative Therapies Group

Dr. Lance Zirpel described a project to improve InterStim Therapy (i.e., sacral neuromodulation [SNM]). The hypothesis is that neuromodulation effects are linked to a specific phase or phases of the bladder filling and voiding cycle. Preliminary data showed significant increases in bladder capacity when SNM is applied continuously in the latter half of the filling cycle in anesthetized rats. He explained Medtronic's vetting process for new ideas or concepts, which involves first testing a data-driven hypothesis in a rodent model. If the results are promising, studies will be conducted in a large-animal model. If the animal model results are positive, then feasibility studies will be conducted. Dr. Zirpel detailed two experiments performed in a large-animal model. The first approach—to establish baselines using three cystometry

studies—revealed that SNM applied during the last 50 percent of the filling phase significantly increased bladder capacity. In a second systematic approach using deep brain stimulation, the SNM also significantly increased bladder capacity, although the overall effect was not as pronounced. Dr. Zirpel pointed out that Medtronic's Summit Research System will automate these types of experiments. An investigational new drug (IND) application will be submitted to the FDA. He noted the efforts to implement the Summit Research System in the bovine urological model and its applications for individualized therapy based on intercontractile intervals.

Reference

1. Brink TS, Zimmerman PL, Mattson MA, Su X, Nelson DE. A Chronic, Conscious Large-Animal Platform to Quantify Therapeutic Effects of Sacral Neuromodulation on Bladder Function. *J Urol* 2015; Vol 194(1):252–258. doi.org/10.1016/j.juro.2015.01.109

Developing Individualized Treatments for Urinary Incontinence: FDA Considerations
Roger Wiederhorn, M.D., Medical Officer, Division of Bone, Reproductive, and Urologic Products, FDA

Dr. Roger Wiederhorn discussed FDA's drug approval process and initiatives to address individualizing UI treatment. He explained that FDA's first contact with a new drug is through the IND application process, which collects information on the clinical protocol, manufacturing, pharmacology and toxicology, and prior experience in animals. The drug or biologic product begins Phase I trials to estimate the initial safety and efficacy, potential therapeutic benefit, and pharmacokinetics and pharmacodynamics in a limited number of human participants. Phase II trials are controlled clinical trials to collect efficacy data on affected individuals with the disease condition and to determine doses for Phase III trials. In Phase III trials, common short-term side effect data are collected. Once Phase III trials are completed, the sponsor submits a new drug application (NDA) that initiates a multidisciplinary review of the Phase III trial efficacy results and data on safety from all clinical trials. The NDA review process results in physician labeling consisting of prescribing information and patient labeling.

Dr. Wiederhorn pointed out that intrinsic (e.g., age, gender, genetics, and race) and extrinsic (e.g., drug-drug interactions, environment, and social behaviors) factors are the first steps to consider when individualizing therapy. The FDA has worked to advance personalized therapeutics and diagnostics by setting the stage for targeted drug development, the drivers and the considerations. For example, genomic findings from FDA-approved drugs for cancer and cystic fibrosis have taught lessons that can be built upon. Biomarkers can enrich the population being tested, characterize the biomarker-negative population, and influence the design of new thresholds. In addition, the FDA is working to give patients a greater voice in the medical product development and evaluation process, and this effort holds immediate promise for patient-reported outcomes to evaluate treatment.

References

1. Tool Kit for Clinical Researchers. National Institute of Dental and Craniofacial Research website. www.nidcr.nih.gov/research/toolkit. Last updated July 21, 2016.
2. Hunter L et al. Engaging Patients across the Spectrum of Medical Product Development; View from the U.S. Food and Drug Administration. *JAMA* 2015; Vol 314 (23):2499–2500. doi: 10.1001/jama.2015.15818

Moderated Discussion and Audience Questions and Answers

Dr. Damaser asked Dr. Tang whether the patients who did not meet the criteria for a targeted treatment responded to the standard treatment and what the options for individuating these patients' care were. Dr. Tang responded that it is not always clear whether the treatment benefits or harms the patient.

Improved monitoring methods unexpectedly reveal that the benefits do not always outweigh the risks. The FDA-approved hemodynamics monitor is one example of this. In some cases, the biological signals can inform the appropriate optimizations. Dr. Tang commented on the unmet need of some patients who may not be responsive to current therapies, which should prompt further development of novel treatments.

Dr. Anna Nagle asked Dr. Wiederhorn about the ability to determine when an adverse event is related to the drug or study and did not occur randomly. Dr. Wiederhorn explained that the Phase III trials are controlled studies in which the treatment effect is compared to a placebo group.

A participant asked Dr. Chancellor about the population that would most benefit from AMDC therapy. Dr. Chancellor responded that those studies have not been done. He noted the recent findings that showed enhanced improvement in women treated with AMDC who had recurrent or persistent SUI after surgery, suggesting that a more damaged muscle would be more receptive to regenerative therapy.

Dr. Nardos asked Dr. Wiederhorn whether new drug clinical trials sought to enroll participants who were representative of minority populations and whether those studies included the appropriate level of statistical power to detect adverse effects in subgroups. Dr. Wiederhorn was not aware of a formalized process regarding new drug trials and representation of minority groups, in general. He noted that data on demographics of the population tested are being captured. FDA would investigate any known metabolic differences related to genetics and new drugs. The sponsor would be the first to identify and document such a relationship.

Dr. Ronald Wood elaborated on the challenge to bring medications to market in the academic setting, given the steps necessary for a translation to the pharmaceutical industry, as outlined by Dr. Heaton. After having investigated in-use medications, Dr. Wood wondered about strategies to reassure the pharmaceutical industry that new indications for existing drugs will not compromise the current revenues. Dr. Heaton suggested establishing mechanisms and key people to interact with potential investors and to consider the technology transfer office as a resourceful mediator. Dr. Heaton also remarked that academic investigators remain at the forefront of new drug discovery and commercialization.

Dr. Mario Romero-Ortega asked Dr. Zirpel how the sensory signals were distinguished from the motor signals in the SNM closed-loop system. Dr. Zirpel responded that the Medtronic Restorative Therapies Group is partnering with investigators in academic to better understand these signals in context. A sacral nerve signal is not the only event that would be recorded in this distributed SNM closed-loop system. For example, other groups have decoded the signals emanating from the dorsal root ganglion that indicate bladder function, which would be entered as an event in this model.

Team-Based Research Planning Session and Working Lunch
Moderator: Carolyn Best, Ph.D., American Urological Association

Participants worked in teams to develop a research plan from the research questions. Meeting speakers and NIH staff were available to provide feedback and answer questions.

Meeting Adjournment

Dr. Bavendam thanked the attendees, moderators, and speakers for participating in the meeting. She adjourned the meeting at 1:15 p.m. EST.