2025 CAIRIBU
Research Strategy Sprint

Friday and Saturday
July 18-19, 2025

UROBIOME RESEARCH INTEREST GROUP

WHO's WHO?

Nicole Gilbert, PhD

Assistant Professor

- Wash U School of Medicine
- Department of Pediatrics
- Department of Molecular Microbiology
- Department of Obstetrics and Gynecology
- Center for Women's Infectious Disease Research

✉ gilbert@wustl.edu

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Emily Coffey, DVM, PhD.

Assistant Professor

- University of Minnesota
- Veterinary Clinical Sciences Dept

✉ coffe099@umn.edu

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Nicole J. De Nisco, PhD

Position

- The University of Texas at Dallas
- Department on Biological Sciences

✉ nicole.denisco@utdallas.edu

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Aaron W. Miller, PhD.

Position

- Cleveland Clinic
- Urology; Cardiovascular and Metabolic Sciences

email@email.net

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Lisa Karstens, PhD

Position

- Oregon Health & Science University
- Division of Oncological Sciences,
- Division of Urogynecology,
- Division of Informatics, Clinical Epidemiology, and Translational Data Science (pending)

Karstens@ohsu.edu

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Tanya Sysoeva, PhD

Associate Professor

- University of Alabama in Huntsville
- Department of Biological Sciences

tas0046@uah.edu

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Chelsie Armbruster, PhD

Associate Professor

- Jacobs School of Medicine and Biomedical Sciences, SUNY Buffalo
- Department of Microbiology and Immunology

✉ **chelsiea@buffalo.edu**

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Vanessa Hale, MAT DVM PhD

Associate Professor

- Ohio State University
- Veterinary Preventive Medicine
- Acting Director, Center of Microbiome Science

✉ **Hale.502@osu.edu**

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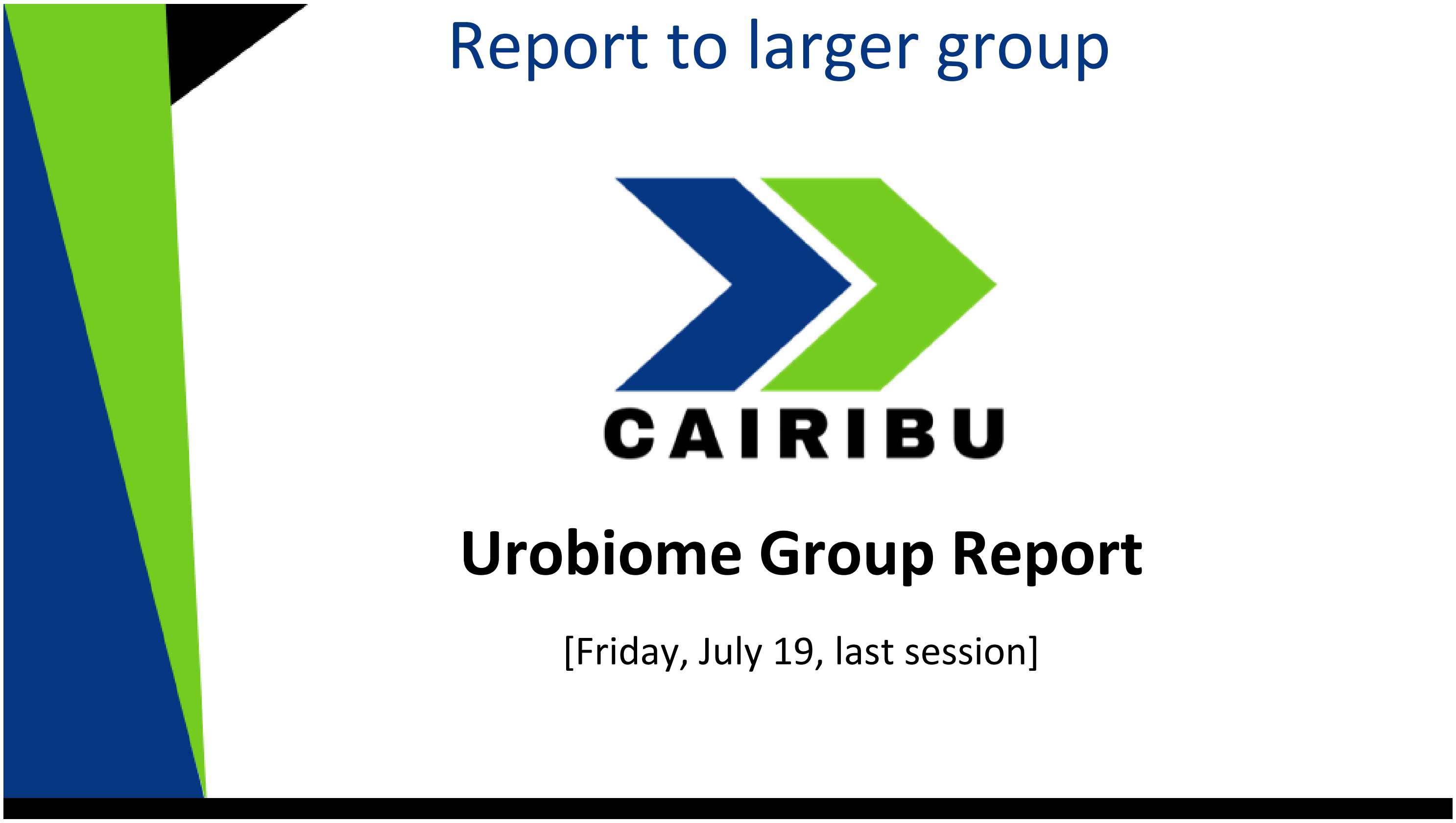
Summary from Day 1

Report to larger group



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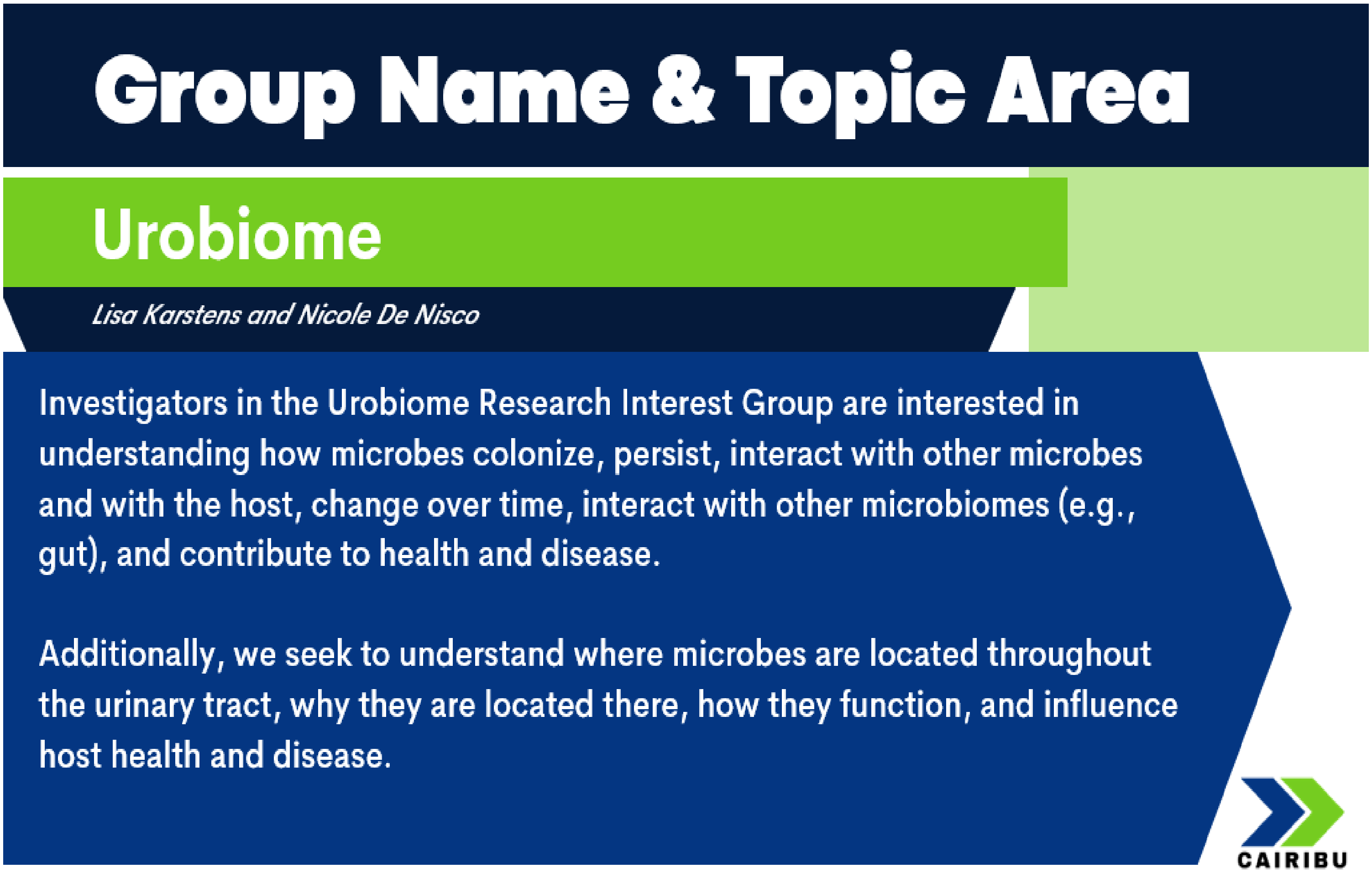
Urobiome Group Report

[Friday, July 19, last session]



Group Name & Topic Area

Urobiome

Lisa Karstens and Nicole De Nisco

Investigators in the Urobiome Research Interest Group are interested in understanding how microbes colonize, persist, interact with other microbes and with the host, change over time, interact with other microbiomes (e.g., gut), and contribute to health and disease.

Additionally, we seek to understand where microbes are located throughout the urinary tract, why they are located there, how they function, and influence host health and disease.

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Critical Gaps in Knowledge

Factors influencing colonization dynamics

- If we want to develop treatments and diagnostics, need to understand microbial colonization needs
- Could understand how to modify the host environment

Functional characterization of host and microbe

- Who is there is not enough; need to know what they do
- Could better target microbes that are pathogenic and promote those that are beneficial; could also be beneficial for profiling, biomarkers, risk stratification

Clinical applications

- How to translate bench to bedside; make science actionable for clinicians and patients
- Basic science should inform clinical practice

Lack of knowledge for what constitutes health and disease

- What actually needs intervention? All mechanistic studies build upon what is "normal" or healthy
- Could work on a review together to identify what we do and don't know

Research Barriers

Model systems

- Current animal models do not recapitulate the human urogenital environment
- We could better model uromicrobiota interactions in a complex host environment for discovery of therapeutics and functional understanding

References and resources

- The reference databases that underly computational methods often do not include urobiome species, meaning that they will not be correctly inferred/ the results will be inaccurate
- Higher confidence in the findings

Clinical acceptance, collaboration, interactions, advocacy

- Acceptance of the urobiome among clinicians (urine is sterile), understanding of beneficial versus pathogenic microbes in clinicians and patients
- Not misdiagnose and overtreat LUTS

Diagnostic imprecision, heterogeneous expression

- LUTS are highly prevalent but often ill-defined, heterogenous and clinically challenging to manage
- Better classification and more personalized treatments

Summary from Day 2

Report to larger group

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Urobiome Group Dissemination

[Saturday, July 19, last session]

Cross Fertilization & Collaboration

Uro-Voiding

- **Non-invasive markers for voiding functionality**
- **Molecular features of each condition that may be used to inform models**

Uro-Aging

- **How does the urogenital environment change over the lifespan?**
    - Intersects with ALL groups
    - Barrier function, hormones, metabolites
- **How to define healthy aging?**

    What if healthy urogenital tract but has other comorbidities, for ex?

Prioritized Research Questions

- **Urobiome Modification**
  - (1) Establish what is healthy
  - **(2) Canine FMT colonization and engraftment study** – how donor bugs transfer to different sites (multi-site sampling, metagenomics, longitudinal)
  - (3) Canine clinical intervention for UTI (and in future, urolithiasis
  - (4) Probiotics as means of modification……..
  - (5) Comparative colonization study with multi-site sampling, longitudinal, deep metagenomic sequencing, different ages?
- **Urobiome Models – In silico and in vitro**
  - (1) Chemical microbe host interface
  - (2) Model estrogen influence on urobiome and urothelium
  - (3) Pair urobiome composition with molecular features
- Multi-Center
  - (1) De novo define what is healthy, disease (agnostic approach)
  - (2) Biomarker-driven, urobiome just one piece
  - (3) Multiomics – agnostic clustering, then dive deeper into each cluster to identify sub-clusters
  - (4) Lots of different data collected
  - (5) BROAD enrollment
  - (6) Maybe longitudinal? Though probably separate study

Prioritized Projects to Develop

- Each individual in the group will have a project
- The multi-center idea will be developed further by those in this group

• GROUP:	(Invited but unable to participate):
• Lisa Karstens	- Maria Hadjifrangiskou
• Nicole De Nisco	- Naz Siddiqui
• Chelsie Armbruster	
• Aaron Miller	
• Nicole Gilbert	
• Vanessa Hale	
• Tanya Sysoeva	
• Emily Coffey	

Knowledge Gaps: Identified in first session on Friday (categorized)

Knowledge gaps and research needs according to the categories created in Google Doc after everyone added their thoughts	Whose idea?	Signed on	Signed on	Signed on	Signed on	Microbe microbe intxns	Factors influencing colonization dynamics	Methods	Host-microbiota intxns	Functional characterization	Geography	Models	Clinical
Molecular triggers for biofilm formation in the urinary tract	Aaron					x							
Metabolic cross-feeding between members of the urinary microbiota	Nicole D					x							
Cross-feeding between microbiota and potential pathogens	Chelsie					x							
Direct cell interactions and metabolite dependent	Tanya					x							
Titrate pathogen burden in gnotobiotic mice and single-cell-profile to the urothelium to generate quantitative dose–response models linking load to innate and adaptive outputs along with urologic phenotypes (i.e. calcium oxalate crystal formation)	Aaron					x							
Are any of the associations between urobiome composition and urologic diseases a consequence of an altered environment? (the chicken-and-egg question)	Nicole G	Lisa					x						
Hormonal regulation of urinary microbiome colonization dynamics in women (especially associated with menopause)	Nicole D	Lisa					x						
Bacterial flows through the urinary tract: Direction, timing & succession of microbes migrating from reservoirs (skin and periurethra, gut, vagina) to bladder/kidney	Vanessa	Nicole G	Emily				x						
Microbial colonization and persistence in the urinary tract	Emily	Nicole G					x						
In germ-free mice, using genetically engineered green and red fluorescent proteins in bacteria - track colonization through blood (i.e. gut origin) and urethral routes (i.e. skin origin) (i.e. same bacterial species - blood bacteria are red; urethral bacteria are green). Distinguish bottom up vs. top down colonization routes and where bacteria end up	Aaron	Vanessa	Nicole G				x						
Exposome in the bladder: Many exposures get processed through the bladder - Diet, xenobiotics, pollutants. How are these layering on with immune cells/microbes/host cells to influence bladder health?	Vanessa						x						
Impact of catheterization (transient vs long-term) on microbiome composition, urothelium regeneration, and susceptibility to pathogen colonization. How long-lasting are the impacts of short-term catheterization? Can this be mitigated by different types of catheters (silicone vs latex, anti-fouling, etc)	Chelsie						x						
Standardizing methodology and best practices, ongoing refinement of low biomass data handling, contaminant IDs, bioinformatic training	Emily	Lisa	Vanessa					x					
Resources and databases to underlie computational models	Lisa							x					
Methods for examining virus/fungi/parasite nucleic acids in addition to bacteria								x					
Which urobiome bacteria are directly responsible for disease features?	Nicole G, Chelsie	Lisa	Emily	Tanya	Tanya					x			
Which bacteria are selected by urinary tract environment based on their stress resistance, interactions, and metabolism	Tanya	Nicole G								x			
Metabolic requirements of urogenital lactobacilli within the urinary and vaginal niches	Nicole D	Tanya	Lisa							x			

Changes in metabolism, virulence/colonization factor expression by bacteria as they move in and out of the urinary tract (e.g. gut or vagina to periurethral area to urethra to bladder)	Nicole G									x			
Does composition change between urethra, different regions of the bladder, ureters, different regions of the kidneys?											x		
How representative is urine of the complete urinary tract composition?											x		
Which microbes tend to be exclusively extracellular vs forming intracellular communities?											x		
How can we best combine of *in silco* modeling to predict microbe/host/bladder health outcomes iterating with high throughput *in vitro* experiments to refine the models which would, in turn, (ideally) allow us to narrow the hypothesis space (for microbes and metabolites) for further *in vitro / in vivo* testing?	Vanessa											x	
Is there a consensus on approaches / limitations / or what advances are needed to study the urobiome in animal models?	Nicole G											x	
Can we develop a dual oxic/anoxic urine-tolerant human organoid model for studying microbiota-host and microbe-microbe interactions?	Chelsie											x	
If and how can we modify the urobiome, using diet, probiotics, novel biotherapeutics like FMT/BMT, etc	Tanya	Emily	Vanessa	Nicole D	Lisa								x
Improving estrogen hormone therapies for better modulation of urogenital microbiome during and after menopause for better disease outcomes (vaginal estrogen only works in about half of women right now…)	Nicole D	Lisa											x
Identifying the "actional component' of the urobiome	Lisa	Nicole G											x
Do fluctuations in bacteria/fungi/viruses/parasites correspond to clinical outcome risk, or can this be used to stratify patients for monitoring/treatment strategies? Would require longitudinal monitoring at short intervals over prolonged follow-up times. Ideally multi-omic approach to better define clinical outcome of interest.	Chelsie												x
Suggest to re-Define/break UTI by some markers/types of damage and pathogen from available data	Tanya												x
Does the urobiome help in refining phenotypic subtypes of lower urinary tract disorders?	Lisa												x
Point of care diagnostics that can predict SYMPTOMATIC UTI now that we know urine is not sterile - using host inflammatory markers AND microbial markers	Nicole D												x
Diagnostic/feasible approaches of sampling for basic science vs clinical disease presentation													x
How does the urinary microbiota contribute to urothelial barrier function?	Nicole D	Nicole G											
Does urinary microbiota modulate host response?									x				
Mouse, bioreactor, biochemical, and cell culture models of bacteria and bacterial metabolite impacts on urologic-specific outcomes (biofilm formation, crystal formation, cellular invasion, inflammation, etc.)	Aaron								x				
How does the urinary microbiota influence bladder pain responses? (microbial metabolites interacting with DRGs, etc.)	Nicole D								x				
How does disruption of urothelial barrier feedback to promote colonization?	Nicole D								x				
How does the urinary microbiota influence urothelial repair and adaptive immunity following a UTI?	Nicole G								x				
How can we determine which models are more/less "translatable" to human health, i.e., determining model value	Emily												

Participants: Name, institution, research focus & topics

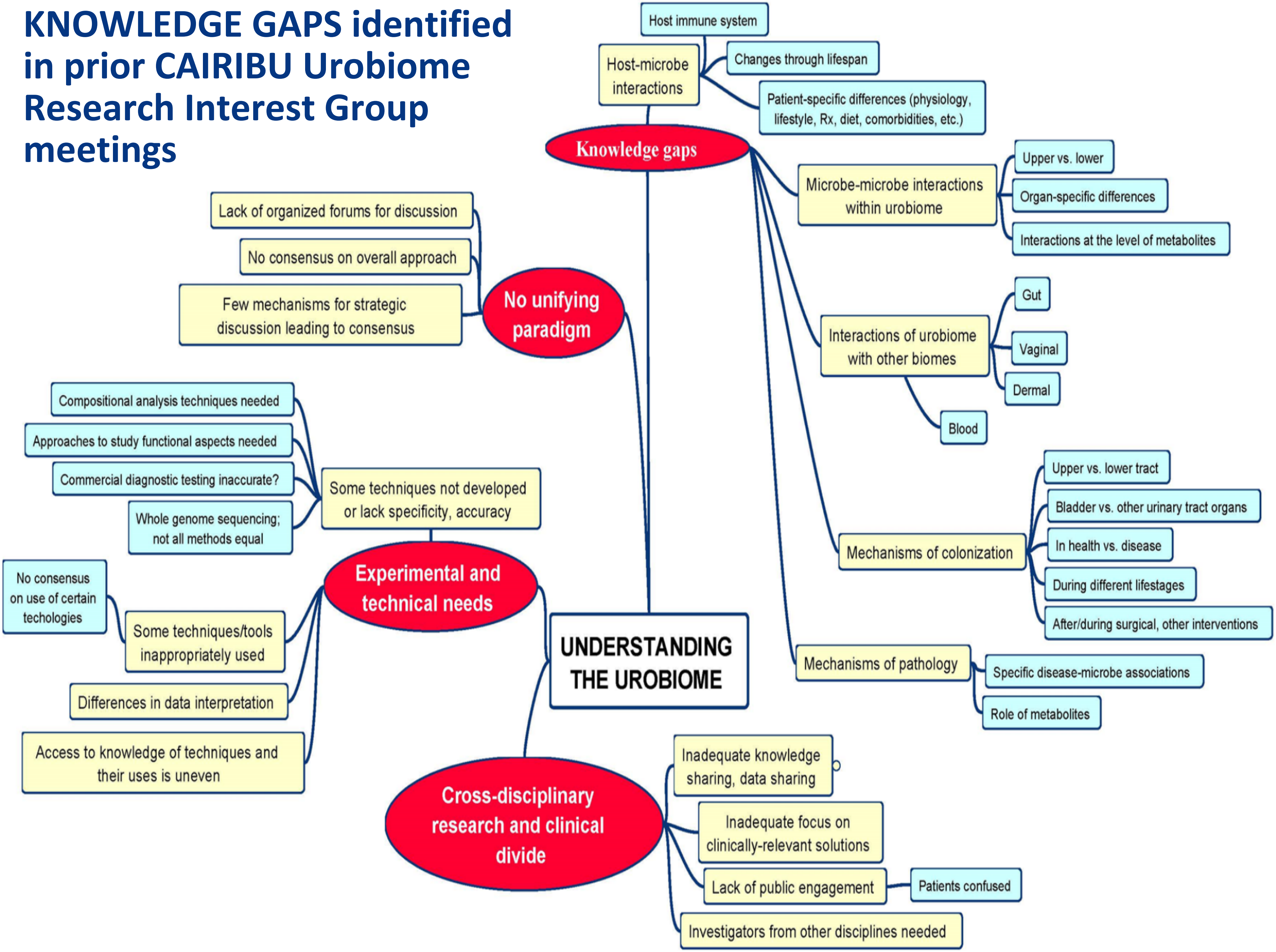
FIRST	LAST	INSTITUTION & DEPT/DIVISION		RESEARCH FOCUS AREAS			PRIMARY TOPICS		
Chelsie	Armbruster	SUNY Buffalo School of Medicine	Microbiology and immunology	CAUTI	Bacteriuria vs. infection	Polymicrobial interactions	Clinical outcomes of polymicrobial interactions	Microbial adaptation during persistent colonization	Aligning urobiome dynamics with signs & symptoms
Emily	Coffey	University of Minnesota	Veterinary Clinical Sciences	Urolithiasis	Gut-urobiome axis and FMT	UTI	SCFAs and stones, downstream urobiome composition	Calcium metabolic pathways in the gut and urinary microbiomes	
Nicole	De Nisco	UT Dallas	Biological Sciences	Recurrent UTI	Urogenital microbiome	UTI diagnostics and therapeutics	Mechanisms of rUTI susceptibility	Postmenopausal women	Metabolic interactions, host-microbe
Nicole	Gilbert	Washington University School of Medicine	Pediatrics, Molecular Microbiology, OBGyn	Vaginal microbiome and UTI	Mouse modeling of female UTI and co-infections	Analysis of clinical samples (vag swabs, urine)	Vaginal microbiome, BV	UTI	Adverse pregnancy outcomes (FGR, SGA, IUGR)
Vanessa	Hale	Ohio State University	Veterinary Preventive Medicine	Environmental chemical-microbe-host interactions	Companion animal models		Temporal urobiome dynamics	Gut-bladder axis	Microbial metabolism of environmental exposures
Lisa	Karstens	Oregon Health & Science Univ	Oncological Sciences, Urogynecology, Informatics	Non-pathogens in bladder	Bioinformatics	Data science	Women's health	OAB, UI	Data standards
Aaron	Miller	Cleveland Clinic	Urology, Cardiovascular, and Metabolic Sciences	Gut microbiota oxalate metabolism	Complex system modeling	Role of urobiome in urologic health	Biofilm development, prevention	Nutrition and gut microbiota	
Tanya	Sysoeva	UAB at Huntsville	Biological Sciences	Antibiotic resistance	Microbial gene transfer	Microbial interactions	Drug-resistant UTI	Microbe-microbe interactions	Urobiome development

Participants: Name, core knowledge, expertise, skills

FIRST	LAST	CORE KNOWLEDGE & EXPERTISE				
Chelsie	Armbruster	Molecular mechanisms of polymicrobial interactions	Bacterial pathogenesis	Biofilms, catheter encrustations	Antibiotic resistance	Bacterial urease activity
Emily	Coffey	Veterinary medicine	Urolithiasis			
Nicole	De Nisco	Biochemistry	Systems biology	Molecular probes for targeted ablation of cystitis	UTI biomarkers, POC biosensors	
Nicole	Gilbert	Molecular biology	Microbiology	Gardnerella, UPEC		
Vanessa	Hale	Microbial ecology	Veterinary medicine	Animal models		
Lisa	Karstens	Bioinformatics	Study design	Coding (R, python, command line tools)	Metabolomics	
Aaron	Miller	Microbial ecology	Math modeling	Coding (R, python, Matlab)		
Tanya	Sysoeva	Microbiology	Bioinformatics			

FIRST	LAST	SKILLS SET						
Chelsie	Armbruster	Mouse models (UTI, CAUTI, bacteremia)	Artificial bladder model	TnSeq metabolomics	Proteomics	Metagenomics	SNV analysis	Clinical data, clinical specimens
Emily	Coffey	Multiomics	Translational	Companion animal models				
Nicole	De Nisco	Shotgun metagenomics	Data analysis	Analytical biochemistry	Clinical samples	Genetic manipulation	Cell culture	Mouse models
Nicole	Gilbert	Developing mouse models	Clinical specimen analysis	Anaerobic culturing	Cell culture models			
Vanessa	Hale	Microbiome profiling	Urine processing	DNA extraction	Urothelial tissue culture	Mouse models	Clinical trials	
Lisa	Karstens	Sequencing	Cloud computing	Taxonomic classification	Phylogenetic tree building			
Aaron	Miller	Bioreactors (e.g., wet lab modeling of organ-specific microbial communities)	Urology-specific mouse model development					
Tanya	Sysoeva	Grow aerobic and anaerobic bacteria	Functional studies	Extract and manipulate DNA	Molecular work (cloning, genome editing)	Protein work (isolation, modification, structural classification)		

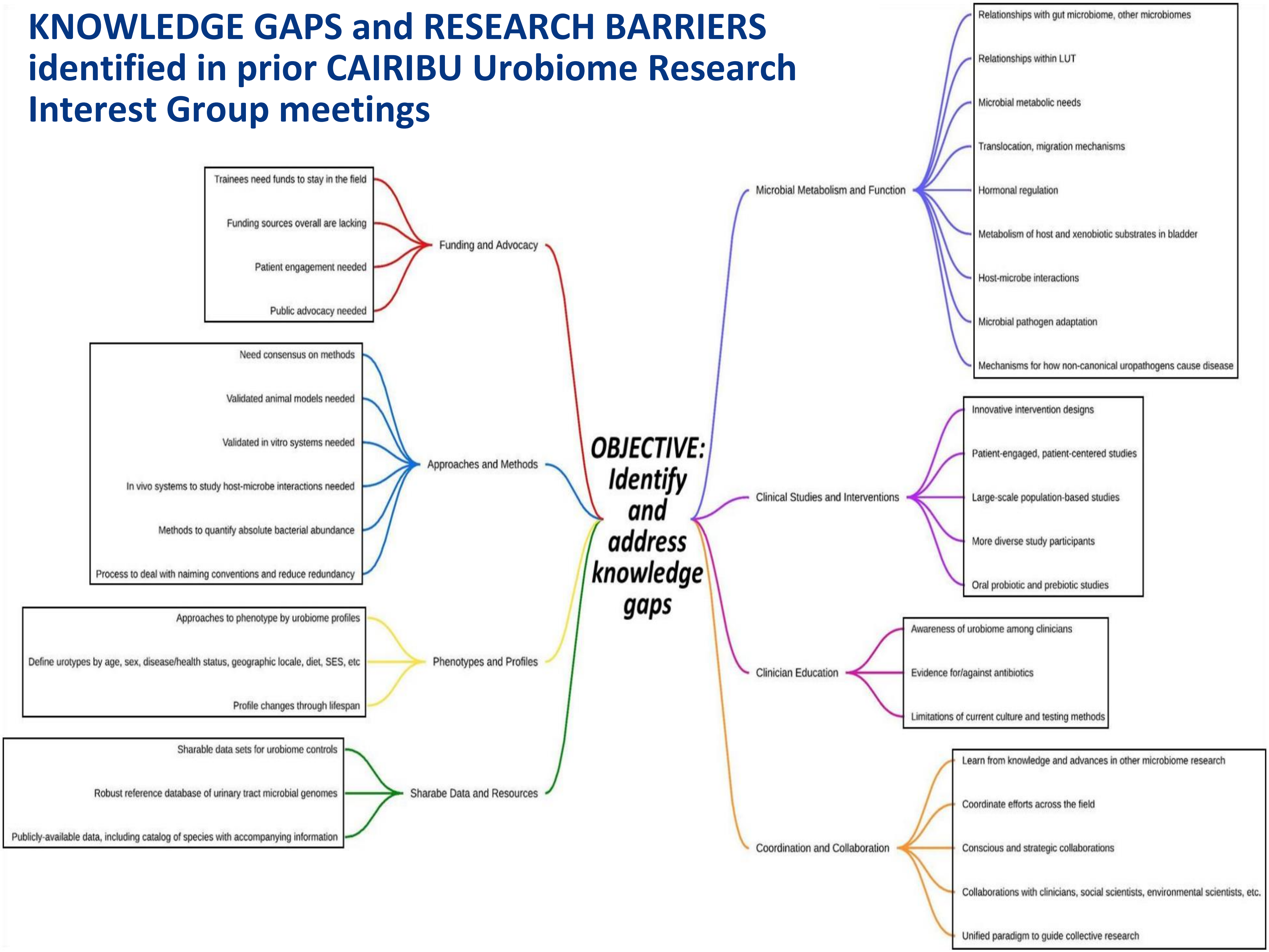
KNOWLEDGE GAPS identified in prior CAIRIBU Urobiome Research Interest Group meetings



UNDERSTANDING THE UROBIOME

- **Knowledge gaps**
  - Host-microbe interactions
    - Host immune system
    - Changes through lifespan
    - Patient-specific differences (physiology, lifestyle, Rx, diet, comorbidities, etc.)
  - Microbe-microbe interactions within urobiome
    - Upper vs. lower
    - Organ-specific differences
    - Interactions at the level of metabolites
  - Interactions of urobiome with other biomes
    - Gut
    - Vaginal
    - Dermal
    - Blood
  - Mechanisms of colonization
    - Upper vs. lower tract
    - Bladder vs. other urinary tract organs
    - In health vs. disease
    - During different lifestages
    - After/during surgical, other interventions
  - Mechanisms of pathology
    - Specific disease-microbe associations
    - Role of metabolites
- **No unifying paradigm**
  - Lack of organized forums for discussion
  - No consensus on overall approach
  - Few mechanisms for strategic discussion leading to consensus
- **Experimental and technical needs**
  - Some techniques not developed or lack specificity, accuracy
    - Compositional analysis techniques needed
    - Approaches to study functional aspects needed
    - Commercial diagnostic testing inaccurate?
    - Whole genome sequencing; not all methods equal
  - Some techniques/tools inappropriately used
    - No consensus on use of certain techologies
  - Differences in data interpretation
  - Access to knowledge of techniques and their uses is uneven
- **Cross-disciplinary research and clinical divide**
  - Inadequate knowledge sharing, data sharing
  - Inadequate focus on clinically-relevant solutions
  - Lack of public engagement
    - Patients confused
  - Investigators from other disciplines needed

KNOWLEDGE GAPS and RESEARCH BARRIERS identified in prior CAIRIBU Urobiome Research Interest Group meetings



OBJECTIVE: Identify and address knowledge gaps

- Funding and Advocacy
  - Trainees need funds to stay in the field
  - Funding sources overall are lacking
  - Patient engagement needed
  - Public advocacy needed
- Approaches and Methods
  - Need consensus on methods
  - Validated animal models needed
  - Validated in vitro systems needed
  - In vivo systems to study host-microbe interactions needed
  - Methods to quantify absolute bacterial abundance
  - Process to deal with naming conventions and reduce redundancy
- Phenotypes and Profiles
  - Approaches to phenotype by urobiome profiles
  - Define urotypes by age, sex, disease/health status, geographic locale, diet, SES, etc
  - Profile changes through lifespan
- Sharabe Data and Resources
  - Sharable data sets for urobiome controls
  - Robust reference database of urinary tract microbial genomes
  - Publicly-available data, including catalog of species with accompanying information
- Microbial Metabolism and Function
  - Relationships with gut microbiome, other microbiomes
  - Relationships within LUT
  - Microbial metabolic needs
  - Translocation, migration mechanisms
  - Hormonal regulation
  - Metabolism of host and xenobiotic substrates in bladder
  - Host-microbe interactions
  - Microbial pathogen adaptation
  - Mechanisms for how non-canonical uropathogens cause disease
- Clinical Studies and Interventions
  - Innovative intervention designs
  - Patient-engaged, patient-centered studies
  - Large-scale population-based studies
  - More diverse study participants
  - Oral probiotic and prebiotic studies
- Clinician Education
  - Awareness of urobiome among clinicians
  - Evidence for/against antibiotics
  - Limitations of current culture and testing methods
- Coordination and Collaboration
  - Learn from knowledge and advances in other microbiome research
  - Coordinate efforts across the field
  - Conscious and strategic collaborations
  - Collaborations with clinicians, social scientists, environmental scientists, etc.
  - Unified paradigm to guide collective research