

# RESEARCH

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Affiliations to disclose<sup>†</sup>:

Nothing to declare

† All financial ties (over the last year) that you may have with any business organisation with respect to the subjects mentioned during your presentation

Funding for speaker to attend:

- Self-funded  
 Institution (non-industry) funded  
 Sponsored by:

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## Outline and Priorities

### Introduction

- Research ethics (**Klausner**)
- Scientific integrity, Rigor, Reproducibility in Biomedical Research

### Evidence (**Dahm**)

- **Determining adequacy of evidence**
- **Ranking evidence (Cartwright)**
- **Review of current systems for evidence assessment (Cartwright)**

### Focus Areas

- Prevention **and intervention** research
- Genomics, Proteomics, Transcriptomics, Metabolomics – pertaining to Incontinence and associated interventions. (**Brubaker**) (**Cartwright**)

### Basic Science (**Burkhard**)

- Laboratory animals and research
- **Model validity for pelvic floor concepts**

### Translational concepts

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## Outline and Priorities

### Clinical Research

- Statistical methods and Study Conduct
- **Protection of subjects and informed consent**
- Special concerns for unique studies
- Experimental devices and materials (**Liao**)(**Boone**)
- Surgical Interventions (**Liao**)
- Recommendations for Surgical and device trials (**Burkhard**)
- Drug trials (**Takahashi**)
- Recommendations for drug trials (**Takahashi**)
- Cost analysis
- Recommendations for cost analysis in pelvic floor trials (**Bo**)
- Recommendations for Special patient groups (**Bo**)
- Recommendations for studies of neurologic populations (**Klausner**)
- Recommendations for studies of faecal incontinence
- Recommendations for of interstitial cystitis (**Takahashi**)
- Recommendations for pelvic organ prolapse (**Takahashi**)
- Recommendations for studies in minors
- Recommendations for basic science research (**Boone**)

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## Research and Balance (Basic / Clinical / Translational)

“Whenever possible, basic or translational research should occur as part of the clinical research study in order to advance discovering of underlying mechanisms or pathophysiology.

This balance between breadth and depth greatly increases the yield of the research effort”

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## Ethics

Acknowledgement of key role for Belmont criteria in human research

Critical need for research outcomes to be generalizable to population at risk

Gender / racial /ethnic / educational / socio-economic disparities have contributed to significant flaws and concerns to substantial subject/topic areas within pelvic health

Absolute need for efforts (at all levels of research) to insure adequate representation of disadvantaged in clinical outcomes and developmental research

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## Evidence Evaluation and Interpretation

Need for improved transparency in outcomes reporting

Value of standardization of evidence aggregation and interpretation thereof

Historical ICUD frame of reference using taxonomy of leveling

*highly recommended, recommended, optional and not recommended*

Subsequently adoption of Oxford Centre for Evidence Based Medicine system

hierarchy of levels of evidence,

subsequent grade of evidence

grades (A to D) based on narrative assessment of the highest level of evidence reported, and consistency of evidence at that level

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## Evidence Evaluation and Interpretation

General acceptance of methodology and reproducibility of same for clinical guidelines

EAU

AUA

Cochrane

WHO

NICE

Grading of Recommendations Assessment, Development and Evaluation (GRADE)

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## Evidence Evaluation and Interpretation

### Certainty of Evidence

High quality systematic review of aggregated evidence

Assessed by accepted tool (AMSTAR-2)

Clearly articulated clinical questions (PICO)

Patients (P), the intervention (I), a comparator (C) and relevant outcomes (O) of interest

Patient centric primary outcomes (delineated list of prioritized outcomes)

Ranked 1- 9 (7 -9 critical importance for decision making)

Use of surrogate outcomes

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## Evidence Evaluation and Interpretation

### Recognized importance of study design

- Study limitations (such as randomization, blinding, attrition bias)
- Inconsistency (validated and non-validated instruments)
- Indirectness of evidence ( different actives compared with sham /placebo)
- Imprecision (sample size, low event rates, or wide confidence intervals)
- Publication bias (negative study bias)

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## Evidence Evaluation and Interpretation

Summary evidence profiles and findings tables

Evidence based recommendations

Strength of recommendations (strong /weak)

Focality of recommendation

- Patients

- Clinicians

- Policy Makers

Determinants of strength

- Balance of desirable / undesirable consequences

- Certainty of evidence

- Patients' values / preferences

- Resource utilization

- Equity, acceptability, feasibility

Final summary statement by panel

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## Basic Science

Importance of animal rights

- 3R principles of animal research (Replace, Reduce, Refine)

Rigorous assessment of new models of toxicologic /teratogenic evaluation

Recognition of limitations of animal models for many pelvic floor conditions

ARRIVE 2.0 (Animal Research: Reporting of In Vivo Experiments) guidelines

- methodological rigour, and reproduce the methods or findings

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## Basic Science

- Species divergences (voiding in rodents v. homo sapiens)
- Lower urinary tract dysfunction ( LUTD) – rodent models
  - Cystometry and validation (awake v. anesthetized)
  - Micturition Video Thermography (MVT) v. spot
  - High frequency ultrasound for assessing bladder and urethral measurements
  - Wireless intravesical real time bladder assessment
- Optogenetic analysis
  - Light responsive proteins
  - Contractility and other smooth muscle functionalities

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## Basic Science

- Models for LUTS and pelvic floor dysfunction
  - Transgenic
  - Unique mechanisms
  - Autoimmune encephalitis
  - Autoimmune cystitis
  - Specific neurogenic models (Parkinson and MS)
  - genes regulation of voiding -acyloxyacyl hydrolase (AOAH)
- Comparability of minipigs to human bladder function
- Sheep (similar neuroanatomy) – value of prolapse and device analysis
- Lack of adequate menopausal model
- Parturition model (distention v. pudendal crush)

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## GENOMICS, PROTEOMICS, TRANSCRIPTOMICS, METABOLOMICS

Multiple areas of evolution

Evidence from apparently acquired diseases such as autonomic degeneration (postural orthostasis, tachycardia syndrome)

Microenvironment of urothelium (cell to cell, cell signaling, interstitial cell function)

Skeletal muscle and collagen diseases (such as Ehler's Danlos syndrome)

Co-morbid diseases (ie diabetes mellitus)

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## Prevention and Early Intervention

Late-stage phenomena often irreversible

Intervention including early life education and alteration of care delivery

Alterations in life-style and life modification (bariatric interventions)

Role of obstetric care changes

Possible earlier intervention for outlet obstruction in men

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Age and ag(e)ing

Longitudinal population studies (BACH)

Social determinants of conditions

Late condition care changes

Hormonal supplementation (both genders)

Cognitive and CNS effects

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Conservative Treatment Trials

Explicit description of intervention being performed

Appreciation of Cognitive Behavioral Therapy (CBT) as component of conservative intervention (short and long lasting and coupled with more intensive interventions)

Documentation of adherence and compliance with planned therapy

Consider value of trial design (such as cross – over, or additive interventions on longitudinal basis)

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## Physiotherapy

Role of behavioral science in life-style change and adherence

Value of adjunctive or additional therapy for pelvic floor therapy (ie electrical stimulation) for UI and POP

Enhanced role of adjunctive assessment methods (manometry measuring urethral, vaginal and anal squeeze pressure, dynamometry, surface, wire and concentric needle EMG, ultrasonography and MRI )

Long term value of therapy

PFMT alone comparable to BF and PFM long term  
favorable to some long term surgical results

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## Pharmacotherapy

New clinical trials have emerged, including stem cell transplantation and intravesical injection of botulinum toxin, which are different from the conventional oral drug therapy. Little is known about the safety, efficacy and tolerability of drug therapy beyond 12-week trials.

Need for long term study of ingestion in real world populations

High anticholinergic load may induce cognitive adverse events in frail elderly with OAB.

Placebo has a role in the improvement of urinary incontinence, supporting the need for placebo control in RCTs.

### RECOMMENDATIONS FOR PHARMACOTHERAPY TRIALS

As effective drug therapy is available for most forms of incontinence, active drug comparator arms are recommended for most trials. HIGH

A concerted effort is needed to create this type of information base. Long-term follow-up of RCT cohorts in an observational cohort is recommended. HIGH

The further studies focused on the anticholinergic load in frail elderly with OAB are recommended. HIGH

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## Interstitial cystitis (IC) / bladder pain syndrome (BPS)

Develop a simple, non-invasive diagnostic tools for HIC and BPS. HIGH

Research that focuses identifying specific pathology (the pathogenesis of a B-cell population abnormality in Hunner lesions) and biomarkers for HIC and NHIC/BPS. HIGH

Standardize the manners of hydrodistension. HIGH

Research to develop a curative treatment for HIC and BPS. HIGH

Establish patient databases in different region and conduct longitudinal follow-up to understand the natural history of the disease and to examine the differences in disease natural history among regions. MEDIUM

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## Surgical and Device Trials

Level 1 evidence priority with rigorous randomization

Long term study plan ( 3 -5 years)

For devices / procedures in trial

- Prospective, RCT (sham or active)

- Rigorous reporting of risks and outcomes

- Consideration of staged adoption of new devices /interventions

- Proceduralist knowledge of condition and technical skill

- Active mentoring with early skills acquisition

- Long term outcomes reporting (registry)

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## Focus for specific groups

Neurogenic patients (inclusive of inflammatory and movement subtypes)

Pediatric

Fail, Older, and Frail older population assessments

Focus on pediatrics

- Long term outcomes of interventions in children/adolescents

- Expanded reporting in transitional conditions and patients

- Awareness of childhood basis of some conditions (such as voiding dysfunction and urinary afferent disorders)

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## Education and Awareness (Continence Promotion)

Informational and educational instruction

- Tailored to population (including factors associated with health literacy)

- Method /channels of distribution (inclusive of social media)

Active engagement of patient focus groups with peer literacy

Underscore importance of practice guidelines (basis) and practice optimization (best practice documents)

Large population assessment of care spectrum and variances

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## Priorities

Continued evaluation of interventions for SUI (both genders)

Assessment of alternative and long-term minimalistic intervention for low to intermediate grade prolapse

Personalized medicine and pelvic floor interventions (inclusive of genetic, congenital, physiologic, hormonal, psychosocial, educational and social support variables)

Investigation in sensory and motor interactions of lower urinary tract and pelvic floor (especially in groups with history of pelvic trauma, sexual abuse, and recurrent urinary tract infection)

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## Research Dissemination /Utility/Generalizability

Role of professional societies in facilitation dissemination  
(i.e. manuscript requirements)

- Compliance with reporting guidelines (CONSORT, STARD, PRISM, SQUIRE)

Feasible

- Widely disseminated
- Research should be HIGH IMPACT
- Wisely use available resources

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## Research Dissemination /Utility/Generalizability

Emphasis on multi –institutional efforts

Methodology, resource, data sharing

Accessibility and interoperability of data storage and management

Use of validated and generalizable outcomes

Strategic resource and operational planning