INUS Neuro-Urology News

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Message from the President

Helmut Madersbacher, MD, PhD INUS President

The first edition of "Neuro-Urology News" was very well accepted, not only by the members of INUS, but also from the befriended societies to which we forwarded the NUN. Prof. Basiri, President of the Iranian Urological Association (IUA), mailed to us "Congratulations, I'm very delighted to hearing such good news. I hope this newsletter will help neuro-urology to grow very fast.", Prof. Jean de la Rosette, General Secretary of Société Internationale d'Urologie (SIU) wrote: "Congratulations on the release of NUN. We appreciate the opportunity to also promote the Société Internationale d'Urologie in this medium."

This second edition of "Neuro-Urology News" will focus on the upcoming INUS Congress in Innsbruck June 9th-11th. The reader will be informed of some of the scientific program highlights, the poster sessions and the workshops. I'm sure that NUN helps us encourage INUS members and members from other societies to attend.



Our interview partners are **Dr. Rose Khavari** working at the Houston Methodist Hospital and our Board-member **Dr. Jorge Moreno-Palacios** from Mexico City.

Dr. Khavari is a leader in neurourology and pelvic reconstructive surgery. She recently published an important paper on Transcranial Rotating Magnetic Stimulation, that can noninvasively and simultaneously modulate multiple cortical regions, demonstrated in women with multiple sclerosis.

Prof. Moreno-Palacios is INUS Board Member since INUS started in 2015 and is responsible for the extensive INUS educational program.

Again, I would like to thank the editor, our colleague and INUS member, **Dr. Glenn Werneburg**, for all his excellent work. I'm sure our readers will enjoy this second edition of "Neuro-Urology News".

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Transcranial Neuromodulation in Neuro-Urology @rosekhavari

Rose Khavari, MD

Dr. Khavari is Associate Professor of Urology and Residency Program Director at Houston Methodist Hospital, in Texas, USA. She is the Director of Research at the Center for Restorative Pelvic Medicine

Associate Professor of Urology, Houston Methodist, USA Glenn Werneburg, MD, PhD, Editor, Neuro-Urology News

This month I had the pleasure of interviewing Dr. Rose Khavari for our Interview with the Expert. Dr. Khavari joins us from Houston Methodist, where she is Associate Professor of Urology and Residency Program Director. Dr. Khavari is Director of Research at the Center for Restorative Pelvic Medicine.

Dr. Khavari received her MD from the University of Texas Medical Branch, Galveston, and did her urology residency training at Baylor College of Medicine. She underwent advanced training in continence, pelvic floor reconstruction, and Neuro-Urology under the mentorship of Dr. Timothy Boone at Houston Methodist Hospital and Baylor College of Medicine. Dr. Khavari is the recipient of multiple awards, including the 2021 Diokno-Lapides Award.

Dr. Khavari has recently been involved in the development and investigation of non-invasive cortical neuromodulation technology to improve voiding dysfunction in individuals with neurogenic lower urinary tract dysfunction. A manuscript from Dr. Khavari's group, published in Journal of Urology this March, reports the results of a derivative of this technology in individuals with multiple sclerosis. In the pilot trial, the therapy was safe and effective, and led to clinical improvements in bladder emptying. In this interview, we discuss the trial, and its results and implications.

Our discussion, edited for length and clarity, is below. A video of the full interview is available at neuro-uro.org and https:// www.youtube.com/watch?v=cQrx-A95akcs&t=7s

Glenn Werneburg: Describe voiding dysfunction and current management strategies for this condition.

Rose Khavari: Historically, "voiding dysfunction" was used broadly to describe a variety of lower urinary tract symptoms. Now, we have a precise definition from the International Continence Society: "Abnormally slow and/or incomplete micturition, based on abnormally slow urine flow rates and/or abnormally high post-void residuals, ideally on repeated measurement to confirm the abnormality." The challenge is that this is difficult to measure, and there is no agreement among experts regarding the absolute value for post-void residual volume or flow rate.

In our investigation, we used accepted definitions that captured individuals with more severe voiding dysfunction. We recruited women with stable multiple sclerosis (MS), and defined voiding dysfunction as more than 40% post void residual volume per bladder capacity. We did not use an absolute value of post void residual volume because many individuals with MS have smaller bladder capacities.

Currently, there are limited treatment options for voiding dysfunction. Alpha-blockers and sacral neuromodulation are therapies that may be offered to a subset of these patients, with varying degrees of efficacy. More commonly, patients require catheterization, which can be a large burden for these individuals. So, for this study we focused on the voiding phase of the micturition cycle.

GW: You used Transcranial Rotating Permanent Magnet Stimulation (TRPMS) in your study. What is this technology and how does it improve upon previously reported modalities, such as transcranial magnetic stimulation (TMS)?

RK: There are different noninvasive brain stimulation modalities on the market. Transcranial magnetic stimulation (TMS) is one of the more commonly used modalities, with more data supporting it. It is a fairly large figure-of-eight coil, which is held over the scalp, and its frequency and intensity are adjusted to deliver either an excitatory or inhibitory stimulus.

Another version of this modality is repetitive transcranial magnetic stimulation (rTMS). This allows for a cycle of repeated stimulations, and this modality is in current use for depression, stuttering, stroke recovery, and other psychological and neurological conditions. There were two small older studies that suggested that this technology could potentially affect lower urinary tract function. We knew that there is not just a single region that controls voiding, but a series of regions that work together as a network. These may be connected anatomically, functionally, or both. Thus, when we were considering modalities, we preferred one that could modulate multiple regions.

Transcranial rotating permanent magnet stimulation (TRPMS) was developed at Houston Methodist, and it recently was used in a trial for stroke recovery, with impressive results. The technology allows for up to six small magnetic devices, which can be placed according to brain regions of interest. In addition, it is portable, and allows for excitatory and inhibitory modulation at the same time. It allows for a depth of about 2 cm, which is sufficient to target our cortical areas of interest. For these reasons, we chose this technology for this collaborative investigation. (continued on page 3)

GW: Describe the design of your study using technology. this

RK: This was a pilot study, funded by a K23 Award from the United States National Institutes of Health.

The first portion of this study was to identify the regions that are superficial enough to modulate using this technology. We know that the voiding centers - the periaqueductal gray and the pontine micturition center - are within the brainstem. However, these are deep, inaccessible, and sensitive, and are involved in circulation and breathing. So, we were interested in identifying surrogate brain regions that could indirectly modulate the brainstem. Next, we were interested in using TRPMS to noninvasively modulate these regions, and determine its safety, feasibility, and efficacy of modulation. Finally, we were interested in whether this modulation might improve urinary symptoms.

GW: What were the main results of the study, and was your team surprised by any?

RK: We found that our modality was safe and feasible. There were no adverse events in the group studied. Of the regions we modulated, there were regions that had significant changes in their activation patterns. These regions included the inferior frontal gyrus and supplementary motor areas. The changes in these areas mimicked the patterns seen in individuals with MS without voiding dysfunction.

Clinically, 6 of the 10 participants in the study met our criteria for response. They had significantly improved post-void residual volume per bladder capacity as well as neurogenic bladder symptom score.

We were surprised to see that, on post-intervention analysis with fMRI, many of the deeper regions of interest were changed in their functional activation, despite not having been directly modulated. These areas are involved in bladder control, and their activation supported the notion that there is a network of functional connectivity, and that modulation of surrogate, and more superficial, regions may improve voiding.

GW: What challenges did you and your team overcome to perform this study?

RK: We started recruitment in Summer 2019. We had two individuals recruited at the time of the COVID-19 shutdowns. Participants in this study had to come to our hospital every day for two weeks, and this became very difficult during the

pandemic period. However, by the end of 2020, we were able to complete the study. This was in large part due to the great efforts of my team including Khue Tran and my coordinator, Hamida Rajab.

In addition, there were some technical challenges. Our study involved urodynamics studies in tandem with fMRI. The protocol involved both bladder filling and bladder voiding. The participants already had voiding dysfunction based on our inclusion criteria, so we had to aspirate their bladders and refill multiple times. Aspiration of the bladder via long MRI compatible urodynamics tubing from the fMRI suite to the control room was challenging, especially since we wanted to keep the scan time as short as possible.

GW: Clearly this effort required a team of teams. What other special-ties, besides urology, were represented?

RK: Yes, this was a very collaborative undertaking. First, I'd like to acknowledge my sponsor, the the National Institute of Diabetes and Digestive and Kidney Diseases of the U.S. National Institutes of Health. Houston Methodist Research Institute also provided funding for this project. Dr. Timothy Boone, my mentor, encouraged and challenged me, and instilled and nurtured my interest in neuromodulation. Dr. Christof Karmonik, physicist in neuroimaging, has been involved since early on in the project, including in its design and analysis. Dr. Santosh Helekar (neurostimulation expert), Dr. Ali Jalali (neurosurgeon), Dr. John Lincoln (multiple sclerosis neurologist) also played critical roles. Khue Tran, a bioengineer in my group, and Hamida Rajab, the research coordinator for the study, were also integral.

GW: What are your next steps?

RK: In many ways, addressing the limitations of this study are our next steps. First, as this was a pilot study, there were no power calculations. But this investigation allowed for the preliminary data to design an appropriately-powered clinical trial. The study also did not have a control group. In Neuro-Urology and functional urology, there is a significant placebo effect. In some cases, this can be up to 30-40%. In the neuromodulation literature, there is also a fairly large placebo effect in trials. So, it's possible that a placebo effect may have been present in our study, and how much that accounted for the results requires investigation. So, moving forward, we are interested in performing a randomized, controlled trial with a blinded arm of neuromodulation.

GW: Nearly half of the International Neuro-Urology Society (INUS) members are under the age of thirty-six. Do you have any advice to share with such individuals who are interested in embarking on careers as physician-investigators in Neuro-Urology?

It's great to be a part of an energetic, and forward-looking community such as INUS. Collaboration is the key – don't be afraid to move out of your comfort zone. We train for years to be specialized clinicians, but when we talk to individuals from other fields, we see that many people are working on similar problems, but from different angles. With collaboration, we can put our efforts together and answer important questions that would otherwise be unapproachable. In many ways, the role of the academic Neuro-Urologist can be the bridge between different disciplines. Finally, be resilient. Many grants will not get funded. Many abstracts and manuscripts will be rejected. Learn, improve them, and resubmit.

Further reading

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Meet the Board Member

Jorge Moreno-Palacios, MD, PhD Urologist Unidad Medica de Alta Especialidad Centro Médico Nacional Siglo XX, Instituto Mexicano del Seguro Social, Mexico

Dr. Jorge Moreno-Palacios studied Medicine at the Universidad Nacional Autónoma de México (Mexico City), starting in 1998. He is specialist in Urology (Residency in Unidad Médica de Alta Especialidad Centro Médico Nacional Siglo XXI, Instituto Méxicano del Seguro Social, Mexico City 2005-2009). In 2009, he was International Fellow of Minimally Invasive Urology at Columbia University, New York, USA.

In 2010, he became Associate Professor of Urology in Centro Médico Nacional Siglo XXI, and IMSS head of the Urodynamic, Functional Urology and Neurourology Clinic. He has been a member of the Ethical and Research Committee in the hospital since 2013.

Dr. Moreno-Palacios' academic experience includes Professor of Urology in the Universidad Nacional Autónoma de México and the Universidad Anáhuac. As a postgraduate professor, he has participated in national and international courses (ICS, INUS, CAU) on functional urology, urogynecology, urodynamics, neurourology, minimally invasive surgery and clinical research. Since 2017, he has directed the fellowship program in Neurourology, Functional urology and Urodynamics in the Instituto Mexicano del Seguro Social.

In 2013 he completed his Master's degree in Medical Sciences and in 2019 his Ph.D. in Clinical Research in the Instituto Politécnico Nacional and is now part of the staff professors at the institute. In 2015, he became member of the National System of Investigators of the Mexican National Council of Science and Technology. He also has served as INUS secretary of education since 2016. Dr. More-

Barrie



Glenn T. Werneburg, MD, PhD Editor, Neuro-Urology News

We are pleased to share this second issue of Neuro-Urology News with you. The first issue was a great success, with distribution to 546 individuals, 200 of whom are active members of INUS. The issue was read by individuals from at least 32 countries. NUN was also distributed to INUS partner societies EAN, EAU, EAUN, HUA, ICS, SBU, SIU and TAU. The issue was well-received. Some comments from readers are above in Dr. Maderbacher's message. We encourage recipients of NUN to share the issues with their colleagues. The publication is available free-of-charge to all interested parties via the INUS webpage.

NUN strives to capture the diverse work

and experiences of its global membership. To do so, we have introduced two new sections for the periodical: "Neuro-Urology Around the World" and "Literature Review". In Neuro-Urology Around the World, we invite individuals to provide a snapshot of their experience in neuro-urology in their region or nation, with a focus on unique barriers and methods to overcome them, and how other nations/regions may learn from the experience. In this issue, Dr. Samarinas provides us with an excellent discussion of the Greek experience.

The Literature Review section will include brief summaries of two to three recent ar-

no-Palacios is reviewer Boletín Colegio Mexicano de Urología, Gaceta Médica de México, Cirugía y Cirujanos, Archives of Medical Research, Neurourology and Urodynamics. He has 60 publications in peer reviewed journals and more than 350 citations.

Dr. Moreno-Palacios' main clinical interests are neurogenic lower urinary tract dysfunction (NLUTD), female stress urinary incontinence, voiding dysfunction, and post-prostatectomy urinary incontinence. His current research includes quality of life in patients with neurogenic lower urinary tract dysfunction, and surgical treatment for patients with voiding dysfunction. In addition, Dr. Moreno-Palacios is professor of History and Philosophy of Medicine in Universidad Anahuac and he has published diverse articles regarding the history of urology.

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ticles from the neuro-urological literature of interest to the NUN readership. For this section, we are **interested in contributions from trainees in their residency or fellowship**. This month, we review recent literature on the surgical management for stress urinary incontinence in individuals with neurogenic lower urinary tract dysfunction, and the urinary microbiota's association with NLUTD.

We welcome your contributions to both of these sections, and welcome your sharing this with any potentially interested trainees. Please send proposals to the INUS Office (info@neuro-uro.org).

INUS Annual Congress: Worksho

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Innovations in Neuro-Urology: Past - Present - Future





Dr. Marcio Averbeck Urodynamics, SNM

Dr. Célia Cruz Translational Research

Urodynamics Workshop Dr. Stefania Musco and Dr. Marcio Averbeck

The Urodynamic workshop is an unfailing educational moment during the INUS annual meeting. The goal is to share the standardization in terminology and methodology with a particular focus on the diagnostic interpretation among the different urodynamic patterns depending on the type and level of neurological injury. After a first theoretical part, a second session will be more practical to become familiar with the urodynamic equipment and data reporting. I'm extremely happy to co-chair the workshop with my friend Marcio and I'm sure that both of us will do our best to ensure ample space for discussion and to raise awareness of the educational purposes for young doctors and nurses who are approaching the world of urodynamics in the neuro-urological field.

I look forward to meeting you in Innsbruck

Translational Research Workshop Dr. Celia Cruz and Dr. Monty Hughes

The value of translational research in Urology is indisputable. It is critical for a better understanding of the normal physiology of the lower urinary tract (LUT) and its pathophysiological mechanisms, as well as to identify new targets and develop new tools. Pre-clinical research is crucial for successful clinical studies and implementation of new therapeutic approaches.

This workshop brings together renowned basic scientists, who are experts in ani-



Dr. Monty Hughes Translational Research

mal models of LUT dysfunction and their translation towards clinical applicability. These scientists will present their cutting-edge results and discuss the state of the field and its future directions. Esra Keller (Austria) will focus on new methods to assess LUT function in animals, which is essential to identify pathological changes in bladder and/or urethral activity. Wouter Everaerts (Belgium) will discuss the role of Transient Receptor Potential channels, which are the basis of the sensory systems in the bladder. Katia Monastyrskaya (Switzerland) will address changes in gene expression in the bladder. Using a miRNA profiling approach, Katia has identified molecular signatures of common LUT pathologies, including benign prostatic obstruction. Francis "Monty" Hughes (USA) will discuss inflammation and the central role played by the NLRP3 inflammasome in causing LUT dysfunction in a variety of bladder disorders, particularly obstruction and diabetes. Ana Ferreira (Portugal) will talk about the main changes occurring in the urethra after spinal cord injury. Finally, Célia D. Cruz (Portugal) will discuss the identification of serotonergic cells in the urethra and address their contribution to LUT control.

Neurosciences Workshop Dr. Jalesh Panicker and Dr. Alessandra Franciulli

The Neurosciences workshop at the upcoming INUS Congress promises to be an exciting session that explores the interface between Urology and the Neurosciences.



Dr. Stefania Musco

Urodynamics



Dr. Jalesh Panicker Neurosciences

The session boasts a start-studded faculty from three continents drawn from Urology and Neurology. Bertil Blok will start with an update of our current understanding of the neural control of the lower urinary tract and health and the use of newer imaging techniques. The session will then delve into the impact that neurological and behavioral disorders have on lower urinary tract and sexual functions. LUT dysfunction will rather uniquely be analyzed in the context of a more generalized dysfunction of the autonomic nervous system by Mario Habek in his talk on prodromal autonomic symptoms in neurological disorders. Cecilia Raccagini will be sharing her research evaluating sexual dysfunction in women with multiple system atrophy (MSA), and Ryuji Sakakibara (virtual) will be discussing the relationship between psychological comorbidities and LUTS. The recent uptick in interest around neurophysiology techniques to evaluate the peripheral innervation of the pelvic floor will be discussed by Jalesh Panicker. The impact that anticholinergic agents have on cognitive functions is a hot topic and will be discussed by Blayne Welk. Finally, Alessandra Fanciulli will be discussing personalized management of the neurogenic bladder.

This interactive session is intended for healthcare professionals who have a clinical and/or research interest in Neurourology and co-chairs Jalesh Panicker and Alessandra Fanciulli look forward to welcoming you at the workshop!

Neuro-Urology Around the World: Greece

Michael Samarinas MD, PhD Urology Consultant, UNUFU (GR) Vice-President, ICI IC/BPS panel member Head of the Neuro-Urology and Urodynamics Unit

The selection of Urology as the medical specialty after university studies could be a lifelong choice with a lot of challenges. The interaction of the lower urinary tract with the nervous system and eventually the establishment of neuro-urology as a scientific subject has already been the motive for investigation from the basic science to the clinical and surgical urology. However, the road to neuro-urology is often difficult with specific and non-specific barriers, having to do with the urologists, the urological departments, health units and sometimes with the central administration. The pathway of neuro-urology consolidation in Greece has proven to be labyrinthine, but finally the monster of Minotaur seems to have been injured.

The essential issue for neuro-urology in Greece, but maybe in the whole world too, remains the difficulty of challenging the young urologist to focus on it. The specific features of neurological patients with lower urinary tract dysfunction could be a deterrent factor for a young Greek urologist or a resident before dealing with neuro-urology. It mainly has to do with the lack of education and scientific information in most urological departments in Greek hospitals. Consequently, many urologists have no contact with neurological patients, not always by choice or lack of interest.

Walking deeper inside our labyrinth, we will find the inadequacy of urological departments to establish training programs in neuro-urology either because of inefficacy of funds and poor equipment or due to departmental focus on other urological subjects, such as endourology and robotics, that seem to be more popular throughout Greece currently. The support of the spectrum of functional urology, including neuro-urology, has not been considered as standard for all Greek urological departments. Although the equipment for non-invasive investigation may be present, sometimes it is not even used. Furthermore, invasive urodynamics, neuro-urological interventions and rehabilitation are supported only is specific centers.

Certainly, the difficulty and complexity in promoting neuro-urology in Greece, is also due to the stiffness of central administration, both inside the health units and in the government. Especially after the recent economic crisis in Greece, the funds for the total National Health System have been restricted, and this has been compounded by the COVID-19 pandemic. Despite these barriers, neuro-urology in Greece is developing and has become creative. We must first highlight the specific focus of the Hellenic Urological Association on this issue, creating a separate section for neuro-urology: the Urodynamic, Neuro-urology and Female Urology (UNUFU) committee. This scientific formation is constituted by the most specialized neuro-urologists, with the crucial mission of developing neuro-urology throughout Greece. Under these auspices, neuro-urological centers have already been established in selected urological departments, especially where there are specialized neuro-urologists with adequate equipment. The first official ac-



ademic neuro-urological center has been achieved during the recent past years, marking significant progress.

We have a lot to do to surpass the handicap of the lack of investment on neuro-urology, but the obvious need of the holistic patients' approach, under the creative collaboration among doctors of different specialties, may force the National Health System to redirect its point of view. This could be the light at the end of the labyrinth.

Although we have not beaten the Minotaur yet, we feel that the end is not so far away. Our educational program for neuro-urology is already running, including regular lessons for all urologists, seminars and congresses absolutely focused, challenging especially our younger colleagues. Moreover, we are getting scientifically closer with other relevant specialties, composing medical teams targeting the ideal treatment for neurological patients. We have to keep in mind the respectable scientific work already published by the Greek centers of neuro-urology, to be reassured for the already reported neuro-urological progress in our country.

If someone has something to learn from the Greek experience of developing neuro-urology, it is that even under a lack of funds or even under a urological society with other priorities and possible necessities, neuro-urology could come into the foreground. Maybe, it seems difficult to kill the Minotaur, but the light at the end of labyrinth is visible.



Literature Review

Efficacy and Safety of Surgical Treatments for Neurogenic Stress Urinary Incontinence in Adults: A Systematic Review

Stefania Musco *et al.*, European Urology Focus, online ahead of print.

This systematic review sought to identify the surgical option for neurogenic stress urinary incontinence with the highest efficacy without detrimental effects on urologic function and bladder management. Thirty-two studies with a total of 852 neurourological patients were included. The treatment options included in the review were the artificial urinary sphincter, autologous sling, synthetic sling, adjustable continence therapy devices, and bulking agents.

Of those who underwent artificial urinary sphincter placement, cure rates ranged from 22-100%, and about 1/3 required revision surgery. In those who underwent pubovaginal sling placement, dryness was reported in 83% of cases, and a significant improvement was reported in 87% of individuals who underwent synthetic sling placement. Efficacy following placement of an adjustable continence therapy device was 30%. Bulking agents were associated with a cure rate of 35%. Seventeen percent of individuals underwent a concurrent bladder augmentation procedure (most often at the time of artificial urinary sphincter

Glenn T. Werneburg, MD, PhD

Editor, Neuro-Urology News

placement). The authors concluded that the majority of evidence was based on retrospective studies, and multiple interventions are often required to achieve continence due to detrusor overactivity, low compliance, and/or the onset of complications.

The decision of surgical management type for stress urinary incontinence in individuals with neurogenic lower urinary tract dysfunction is based on many clinical and urodynamic factors, and patient selection is of the utmost importance. The patient population with neurogenic stress urinary incontinence is heterogenous, as are the definitions of success, as the authors point out. The study importantly establishes and summarizes success and complication rates of the different interventions, as well as the high rates of repeat intervention.

Distinguishing Features of the Urinary Bacterial Microbiome in Patients with Neurogenic Lower Urinary Tract Dysfunction Giulia Lane *et al.*, Journal of Urology, 2022. 207(3):627-634.

The authors sought to characterize the urinary microbiome in individuals with neurogenic lower urinary tract dysfunction, and determine differences in urinary tract infection frequency and bladder drainage management. This prospective study included urine from 95 individuals with neurogenic lower urinary tract dysfunction who either had an indwelling catheter or performed clean intermittent catheterization. The Proteobacteria phylum was predominant, and specifically *Escherichia coli* was highly represented. Bacterial alpha diversity was greater in those who had indwelling catheters versus those who performed CIC, and *Pseudomonas aeruginosa* had a higher relative abundance in individuals with indwelling catheters versus those who performed CIC. There were no differences in alpha or beta diversity between individuals with versus without recurrent UTI.

Interestingly, although the most prevalent bacteria present were uropathogens (*Escherichia coli*), there was no difference in the urinary microbiome based on UTI frequency or the use of antibiotic prophylaxis. These findings underscore the need for further work to determine the mechanistic transition between colonization and infection of the neurogenic urinary tract. This understanding will ultimately lead to improved opportunities for detection and drug targeting.





Innovations in Neuro-Urology: Past - Present - Future

Save the date for the Annual INUS Congress at the Kongresshaus Innsbruck, Austria. The congress takes place from June 9th to 11th 2022.

INUS Calendar

INUS Lectures at the 25th Iranian Urological Association Annual Congress Tehran, Iran May 17-20, 2022

INUS Annual Congress 2022 Innsbruck, Austria June 9-11, 2022

American Urological Association Annual Meeting New Orleans, United States May 13-16, 2022

INUS Session at ICS 2022 Vienna, Austria September 7-10, 2022

42nd Congress of the Société Internationale d'Urologie Montreal, Canada November 9-13, 2022



Submit your abstract for SIU 2022!

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