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# MOVING ALONG

International Parkinson and Movement Disorder Society

Editor, Antonio Strafella, MD, PhD, FRCPC

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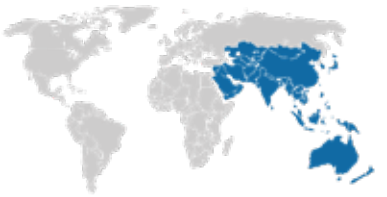

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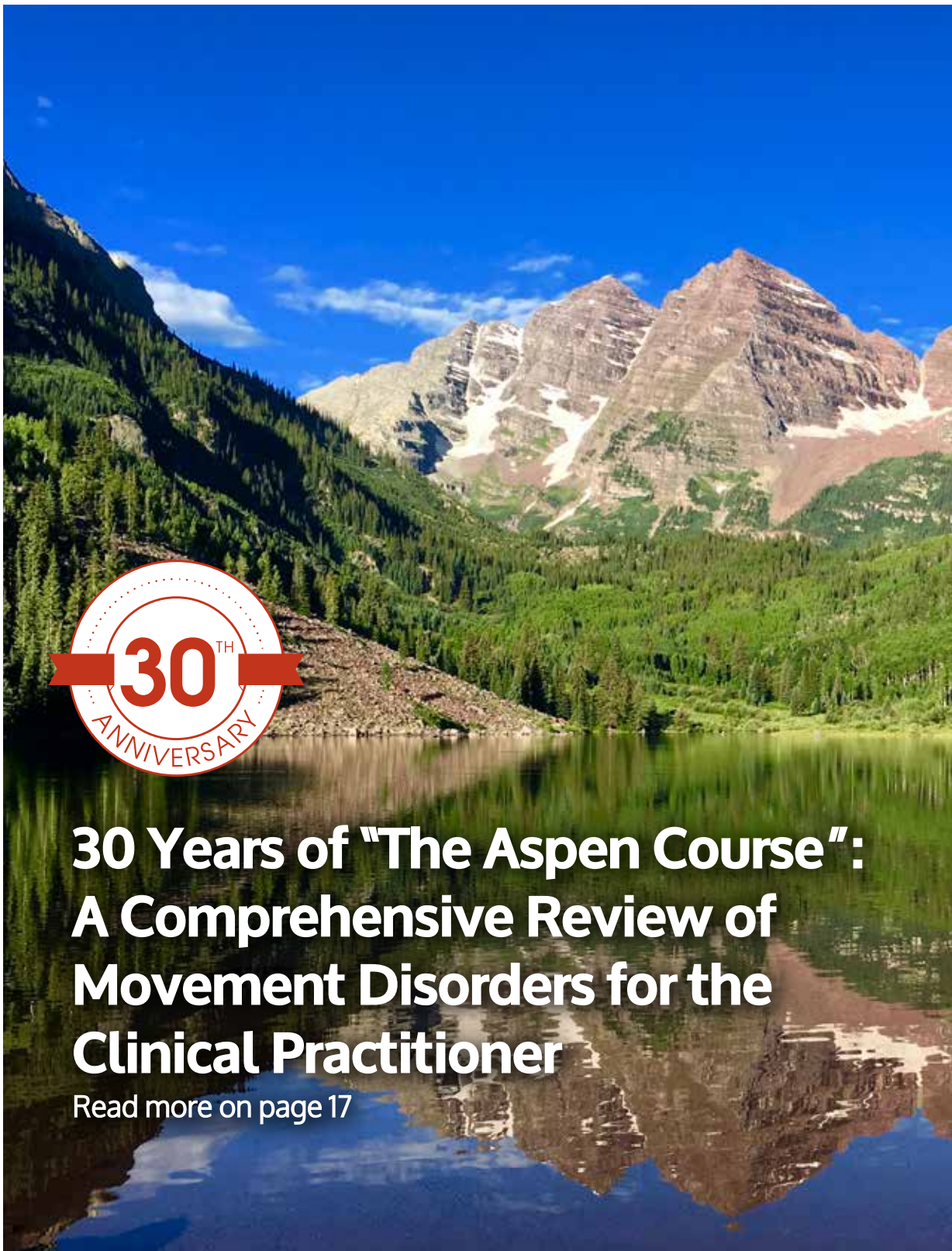


## 30 Years of "The Aspen Course": A Comprehensive Review of Movement Disorders for the Clinical Practitioner

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## Letters to the Editor *Your comments and questions are always welcome.*

### Editorial Policy

As part of its democratic commitment, MDS welcomes the input of all its members about the features and articles that appear in this newsletter. Have a comment or question? Each issue will include responses in the "Letters to the Editor" section. All materials submitted become the property of MDS.

### Address your communications to:

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# Editorial

On behalf of the *Moving Along* Editorial Board, we hope that you and your family members continue to be healthy and safe during this challenging time of the coronavirus (COVID-19) pandemic.

We would like to thank the entire MDS community for the enthusiasm demonstrated in contributing with new exciting content for this new issue of *Moving Along*. The Editorial Board appreciates your participation and worked tirelessly to pull together all of this material. Recently, a new member from the MDS Africa Section joined our editorial board, Dr. Shaimaa El-Jaafary, from Cairo University. We welcome her and look forward to her contribution to the future issues.

2020 was an eventful year for MDS and our members. The historic MDS Virtual Congress 2020 was attended by over 20,000 participants from 145 countries. Congratulations to the the MDS Virtual Congress Task Force for this truly amazing accomplishment. This issue of *Moving Along* features many of the lectures and scientific topics featured during the MDS Virtual Congress, including the Presidential and Junior Award lectures, as well as the Clinical Highlights from 2020. In addition, 2020 marked the 30th anniversary of "The Aspen Course", which was also moved to a virtual format, and Dr. Joseph Jankovic has prepared a fantastic remembrance of the history of this popular event. MDS has a new Basic Science Special Interest Group, and the Chairs have submitted an update on their current and future activities. Lastly, the "President's Corner", by Prof. Claudia Trenkwalder, continues to introduce young members to our MDS community.

We would like to thank the MDS Officers, International Executive Committee, Regional Section leadership, and all of the MDS staff for their amazing support in continuing to make this possible. We hope you enjoy this issue of *Moving Along*, and wish you and your families a safe and healthy 2021!

Warm regards,

Antonio Strafella, MD, PhD, FRCPC
*Moving Along* Editor, 2019-2021

## 2019-2021 Moving Along Editorial Board


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# President's Corner

What a year! As 2020 has come to a close, I would like to take the opportunity to thank each and every one of you for your continued commitment to MDS and to wish you Season's Greetings.

While this past year has been a challenge for all of you in so many ways, we hope that you have continued to receive high quality movement disorders education through MDS programs, which were modified in many ways to help you navigate through these unprecedented times.

What did we change?

- The introduction of an in-depth COVID-19 resource section on the Society website.
- All scheduled live programs and courses moved to an online format, including the Aspen course, which you can read more about on page 17. These changes helped the Society open all education to a larger group of participants than ever before.
- Members and non-members were able to participate together virtually in the International Congress with a record attendance of 20,000 participants with no fee to attend.
- Membership has continued to grow and we ended 2020 with over 11,000 members!

For the first time ever, MDS was able to reach out to all corners of the world with these virtual activities and meet the needs of the changing global climate.

In 2021, the Society will continue this path, as the pandemic is not yet over despite positive news from vaccination strategies. Some of the planned activities include:

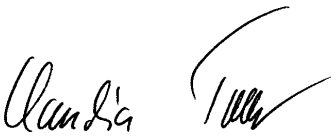
- Continuing to provide virtual education for both global and regional topics.
- Organizing the first ever Virtual AOPMC on June 4-6, 2021.
- The 2021 International Congress will be taking place in a primarily virtual format in September 2021, with abstract submissions opening on January 15, 2021.

MDS remains optimistic that we will be able to see each other in person towards the end of 2021 - if that is possible, we will work on creative solutions to make it happen!

The only way to have a live congress or course again, is to win the battle against the virus with the help of the vaccines. Everyone who is able to get the vaccine, this excellent achievement of science in a short time, please get it to enable live meetings again! To support your colleagues and patients with information and education about the vaccines, we have installed special information and tools on our website.

In conclusion, and with hope for the future of the Society and the field of Movement Disorders, it is my pleasure to introduce two more MDS young members (see page 5).

With this glimpse of hope to a better 2021,



Claudia Trenkwalder, MD
MDS President, 2019-2021

President's Corner, *continued on p. 5*

President's Corner, *continued from p. 4*

**Mariana H.G. Monje MD, PhD**
**Chicago, IL, USA**

I recently started working as a postdoctoral researcher at the Department of Neurology at Northwestern University Feinberg School of Medicine in Chicago, IL, USA.

During the past years, I have had the privilege of combining basic neuroscience research (completing my PhD) with clinical activity, doing a clinical and research fellowship in movement disorders at HM-CINAC, in Madrid, Spain.

As a young neuroscientist, I am moved by a deep interest in the fundamental pathophysiology of movement disorders, especially Parkinson's disease, and the possibility of integrating this knowledge with translational purposes to which I am currently dedicated. As a clinician, I enjoy a comprehensive and holistic approach to the patient assessment: incorporating insights from neuroscience and medical pathology. I am also interested in new technologies and their use in helping the diagnosis, monitoring and treatment of patients with movement disorders. There is so much innate scientific inspiration and learning that originate while taking care of patients!

I joined MDS in 2017, when I was in my last year of residency. I attended the James Parkinson: A Celebration of 200 Years of Progress course in London, and later that year, the 10th Summer School for Young Neurologists in Marburg. They were such inspiring and rich moments that motivated my previous decision to pursue a dual career --as a clinician and as a neuroscience researcher in Movement Disorders. It is not an easy path, but not an impossible one. Since then, I have been pleasantly surprised by MDS' diligent organizational chart and the remarkable capacity to unite specialists and healthcare professionals with interest in movement disorders.

Currently, I have the honor to serve as a member of the MDS-Rating Scales Electronic Development Committee, helping to develop new electronic tools for the common benefit of MDS. To that end, it is great to see how the MDS holds a tremendous potential to execute real actions and plans that translate into clear benefits for all the members and for our clinical practice.

For the upcoming years, the current MDS efforts to intertwine fundamental neuroscience and clinical practice (e.g. the initiative of a new Basic Science member category) will set a precedent that will enrich meetings, facilitate knowledge transfer, and eventually lead to more translational research.

Finally, I think the MDS initiatives for the education, training, and support of the next generation of movement disorder specialists and leaders is a demonstration of the commitment and investment to the future of our field. As Young Members of MDS, it is encouraging to be part of this challenging and exciting roadmap ahead.

**Nirosen Vijiaratnam, MBBS, BMedSci, FRACP**
**Malaysia**

I am Nirosen Vijiaratnam a neurologist from Australia though I was born in Malaysia. I completed my medical, general neurological and movement disorders sub-speciality training in Melbourne, Australia across a number of centres before moving to the United Kingdom. I currently work in the Unit of Functional Neurosurgery at the National Hospital for Neurology and Neurosurgery, Queen Square, and am in the process of completing a PhD in affiliation with the Institute of Neurology at the University College London. Although I have explored a range of interests in the clinical aspects of movement disorders over the last five years, my current clinical and research focus is in Parkinson's disease and in particular disease modification. I am also interested in overall treatment approaches in Parkinson's disease and deep brain stimulation programming techniques in particular.

I joined the MDS during my first movement disorders fellowship in 2015, and gradually became more involved over the years. I am proud to be serving as a member of the Steering Committee of the Young Members Group, which allows me to connect with other young colleagues around the world, and contribute to the expanding MDS educational activities. Along with my colleagues, I was involved in the collation and analysis of the recent web-based survey on the impact of the MDS Schools for Young Neurologists. The findings were recently published on the MDS website. It was reassuring to see the excellent improvements participants reported from this MDS initiative and the work highlighted the merits of the Society's ongoing initiatives to better education in the field and ultimately patient care. MDS has contributed greatly to a strong movement disorders scientific community with an ethos for collaboration and a focus on the betterment of our understanding and treatment of patients. In the current challenging climate, it remains more crucial than ever that collaborations across the globe in basic science, clinical research, and patient care initiatives are strong and MDS will be key in realising these hopes. I look forward to contributing greatly to this and to the good times of the past, where we can all come together annually, as the International Congress has enabled us to before to celebrate the friendship and joy that this Society has encouraged throughout its course.

# MDS Virtual Congress 2020 Presidential Lectures

## Stanley Fahn Lecture

### *Diagnosing Parkinson's Disease - From the Street to the Bench*

*— Werner Poewe, MD, Professor of Neurology and Director of the Department of Neurology, Innsbruck Medical University, Innsbruck, Austria*


As for most neurologists of my generation, who had a special interest in the subspecialty of Movement Disorders, Stanley Fahn has been a master and idol for me from the beginning of my career – a role model I could never hope to come close to match. When I was notified of having been awarded the 2020 MDS Congress Stan Fahn Lecture, it evoked an idiosyncratic and somewhat overwhelming cocktail of feelings, including elements of humility, honor, pride and quite a dose of apprehension – how could my lecture ever do justice to the great man and MDS founding father?

I vividly remembered one of my early personal encounters with Stan in 1985 at a Parkinson meeting in New York, where I presented work I had performed with Andrew Lees and Gerald Stern on levodopa-induced OFF-period foot dystonia. It was in one of the smaller oral presentation breakout rooms and I got quite nervous when I noticed Stan Fahn sitting in the first row. At that time, I would never have imagined that - some 15 years later - this eminent leader in the field would give me a call in his capacity as chair of the MDS Nominating Committee to ask whether I would be prepared to accept a nomination for President of the Society!

Looking back at my career as a clinical movement disorder neurologist and checking topics from my own clinical research that might qualify for a Stan Fahn Lecture, I initially felt tempted to speak about levodopa. When I had first met Stan in the 1980's, I was doing projects on levodopa pharmacokinetics and motor complications in London and many years later we had worked together on the subject as co-editors of a special supplement of the *Movement Disorders* Journal devoted to 50 years of levodopa in Parkinson's disease (PD). Also, more than 50 years after its introduction in PD therapy, levodopa still remains a very actively researched drug with ongoing clinical trials of novel formulations and delivery routes. These were all fitting circumstances to make levodopa the theme of a Stan Fahn Lecture – but I eventually turned to the diagnosis of PD as the theme of my talk for several reasons. First, despite all refinements in diagnostic criteria, the accuracy of an initial clinical diagnosis of PD at first visit remains suboptimal. Second, it has become clear that PD likely begins long before the emergence of diagnostic motor signs and the detection of prodromal stages of the disease is a major need when it comes to implementing disease-modifying interventions. For both reasons, diagnostic biomarkers that aid in early detection and differentiation of PD from other types of degenerative parkinsonism have been a research focus for many groups around the globe, including our team in Innsbruck, for many years. I found it intriguing to follow the evolution of the diagnostic concept of Parkinson's disease as it transitioned from a clinico-pathological entity, anchored on the presence of cardinal motor features and Lewy-body pathology and cell loss in the substantia nigra, towards a complex multidimensional construct, where the synthesis of clinical information with findings from a growing number of biomarker classes – most prominently imaging and genetic and molecular markers – leads to refined granularity of PD diagnosis with enhanced accuracy and sensitivity for the earliest disease stages. As phrased in the title of my lecture, the diagnostic process in PD has thus moved *'from the street'* – where James Parkinson and many subsequent generations of neurologists felt confident in making a diagnosis even from a distance – *'to the bench'* – where biomarkers provide essential information on disease-specific biological alterations enabling early and accurate diagnosis as well as the definition of disease subtypes. Despite of all these developments, diagnosing PD will always require careful and astute clinical observation with attention to detail followed by judicious use of diagnostic tests and their critical appraisal – in other words clinicians typified by the glorious example of Stanley Fahn.

# MDS Virtual Congress 2020 Presidential Lectures

## C. David Marsden Lecture

### *Myoclonus is Telling How Our Brain Works*

*— Hiroshi Shibasaki, MD, PhD, Emeritus Professor, Kyoto University, Kyoto, Japan*

In Washington, DC in 1990


It is my great honor and pleasure to give the C. David Marsden Lecture. My interest in myoclonus dates back to 1971, when I was a resident of Neurology at University of Minnesota Hospital in Twin Cities, USA. The Department Chairman at that time was Prof. A.B. Baker, who founded American Academy of Neurology in 1948. I was strongly influenced by his clinical neurology. After having returned to Japan, I kept my interest in myoclonus. One day in 1975, I was trying to record Bereitschaftspotential (BP, readiness potential) in a patient with progressive myoclonus epilepsy, because I had found that the BP is lost in the lesion of the cerebellar efferent pathway (dentato-thalamic tract). For recording BP, I was back-averaging the EEG preceding self-paced hand movement. While looking at the computer display, I happened to notice of a sharp activity on the averaged EEG instead of BP, which is a slowly rising surface-negative activity. By subsequent studies including magnetoencephalography (MEG), I proved that the activity originated from the contralateral primary motor cortex (M1) and preceded myoclonus of the hand by 20ms. Thus, it turned out to be the result of inadvertent averaging of EEG with respect to myoclonus instead of voluntary muscle contraction. I could have easily missed this serendipitous observation if I was not doing the test by myself.


The above technique was named 'jerk-locked back averaging' by Dr. A. Martin Halliday in 1978, when I was working as a visiting scientist in his laboratory at the National Hospital of Neurology, Queen Square, London, United Kingdom. During my stay in London, I met Prof. Marsden twice; first in Maudsley Hospital and then at Queen Square. We enjoyed discussing the topics of our common interest, including pathophysiology of myoclonus. Now it is our understanding that cortical myoclonus is due to pathological over-excitation of the physiologically existing network involving the primary sensorimotor cortex.

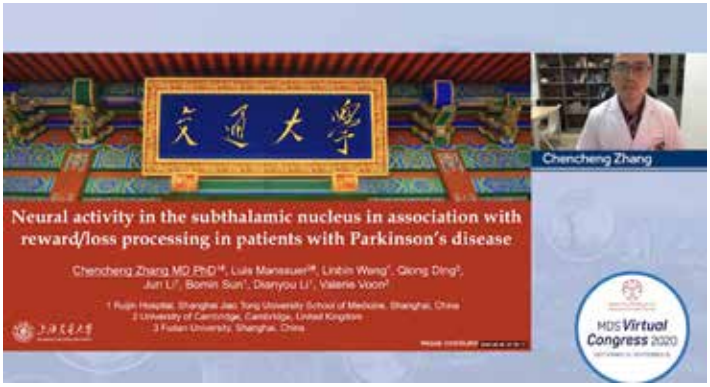
# MDS Virtual Congress 2020: Junior Award Lectures

**Chencheng Zhang, MD, PhD, and Rachel Lawson, PhD were selected for the 2020 Junior Awards at the MDS Virtual Congress. Their award-winning abstracts and research were presented during the Presidential Lectures Plenary Session on Sunday, September 13, 2020.**

## Subthalamic Oscillatory Activity Dissociates Reward and Loss in Parkinson's Disease

— *Chencheng Zhang, MD, PhD, Neurosurgeon, Center for Functional Neurosurgery, Ruijin Hospital Shanghai JiaoTong University School of Medicine; Junior Principal Investigator, Shanghai Research Center for Brain Science and Brain-Inspired Intelligence, Shanghai, China*

*Chencheng Zhang, MD, PhD, is a functional neurosurgeon specialized in Parkinson's disease and neuropsychiatric disorders. He completed his PhD at Shanghai JiaoTong University School of Medicine under the supervision of Professor Bomin Sun. He is currently also a junior principal investigator in Shanghai Research Center for Brain Science and Brain-Inspired Intelligence. Besides the clinical duties and investigation, he is likewise active in the clinical neuroscience experiment via neuroimaging and intracranial electrophysiological approaches. In this study, he would acknowledge the tremendous efforts and support from Prof. Valerie Voon and Dr. Luis Manssuer at the University of Cambridge.*




The subthalamic nucleus is an effective deep brain stimulation target for Parkinson's disease and obsessive-compulsive disorder and has been implicated in reward processing. Patients with Parkinson's can display addictive behaviors related to abnormalities in the processing of rewards and losses. The role of the subthalamic nucleus and prefrontal oscillatory dynamics in the anticipation and receipt of reward and loss is not yet fully understood. Intracranial subthalamic local field potentials from deep brain stimulation electrodes and prefrontal scalp electroencephalography were recorded in 17 Parkinson's patients whilst they performed a monetary incentive delay task. The results showed that delta activity was increased in both the subthalamic nucleus and prefrontal cortex during the anticipation of rewards and losses. In contrast, subthalamic gamma activity was specific to the anticipation of loss. Both subthalamic theta activity to reward anticipation and outcome were associated with greater motivation. During reward outcomes, increased delta-theta activation showed feed-forward connectivity from the subthalamic nucleus to the prefrontal cortex and phase-amplitude coupling to motor-related beta activity within the subthalamic nucleus. In contrast, loss outcomes were characterized by a decrease in delta-theta activity and lower coherence and coupling. Critically, decreased delta-theta activity to loss in the subthalamic nucleus was associated with the severity of impulse control problems. We concluded that subthalamic activity appears to dissociate reward and loss processing. Addictive behaviors are associated with impaired sensitivity to negative outcomes. The results are relevant to identifying oscillatory biomarkers that are potentially responsive to neuromodulation.

## Predicting Dementia in the First 6 years of Parkinson's Disease in the ICICLE-PD Cohort

— *Rachael A Lawson, PhD, Janet Owens Parkinson's UK Senior Research Fellow, Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, United Kingdom*

*Rachael A Lawson, PhD, is a psychologist and a Janet Owens Parkinson's UK Senior Research Fellow based in the Clinical Ageing Research Unit (CARU) in the Translational and Clinical Research Institute, Newcastle University. In 2012, she joined the ICICLE-PD study team to complete her PhD, supervised by Professor David Burn, and is still actively involved in overseeing the study. Her work focuses on neurocognition in people with Parkinson's disease, and with a particular interest on cognitive decline and dementia and in people with Parkinson's disease. She is currently completing a fellowship that aims to improve the recognition of delirium in people with Parkinson's disease.*

Cognitive impairment is a common non-motor feature in people with Parkinson's disease (PD) which has a significant impact on the quality of life of patients as well as their family, friends and carers[1,2]. The development of disease-modifying treatments to slow or stop the progression to dementia are ongoing, but a challenge is identifying patients for clinical trial stratification who may be the most likely to benefit from these therapies, such as patients early in disease or even in prodromal phases[3]. One of the difficulties is that cognitive impairment in PD is heterogeneous, with multiple cognitive domains effected[4,5]. It would, therefore, be useful is know which cognitive deficits are most predictive of developing an early dementia, and what are the optimal cut-offs for specific tests.

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MDS Virtual Congress 2020: Junior Award Lectures, *continued from p. 8*


As part of the ICICLE-PD (Incidence of Cognitive Impairments in Cohorts with Longitudinal Evaluation in Parkinson's disease)[6], we aimed to identify which baseline tests in a cohort of newly diagnosed participants with PD predict the early development of dementia (PDD) within six years, and which were the optimal cut-offs to predict PDD. We recruited 212 participants with PD and 99 age-matched controls. All participants completed a detailed schedule of neuropsychological tests of global cognition executive function, attention and memory at baseline. Participants returned at 18-month intervals for 72 months and PDD was diagnosed using The ***Movement*** Disorder Society criteria.

By the end of the 72-month assessments, 22% of PD participant developed PDD, compared to 2% of controls who developed dementia. To identify which baseline cognitive tests predicted PDD, we performed a series of Cox regressions using a data driven approach, controlling for age, motor severity and genotype. We looked at four different cut-offs, PD performance 1SD, 1.5SD and 2 SD below controls to classify impairment in each test, indicating cognitive impairment above normal ageing, and using the median cut-off, which is commonly used in the literature. We also applied the median of pen and paper tests commonly used in clinic to identify which tests could help identify patients who are likely to develop an early dementia for support and clinical management.

We found that selected measures for global cognition, executive function and attention significantly predicted the development of PDD; however, the specific tests identified was dependent on the cut-offs applied. Using pen and paper tests, impaired global cognition measured using the Montreal Cognitive Assessment (MoCA), pentagon copying and semantic fluency predicted PDD, and could be useful screening tools for routine clinical practice. However, the tests most predictive of developing an early dementia were impaired MoCA, pentagon copying and attention, including reaction time tests and attention accuracy, using median cut-offs.

Our work confirms that previously reported cognitive predictors of PDD, such as semantic fluency and pentagon copying[7], hold true for our new cohort. However, more sensitive measures of attention in addition these may have greater predictive power, and these tests may be more suitable for future clinical trials stratification.

**References**

1. Lawson R, Yarnall A, Duncan G, et al. Cognitive decline and quality of life in incident Parkinson's disease: The role of attention. *Parkinsonism Relat Disord*. 2016;27:47-53.
2. Leroi I, McDonald K, Pantula H, Harbishettar V. Cognitive impairment in Parkinson disease: impact on quality of life, disability, and caregiver burden. *J Geriatr Psychiatry Neurol*. 2012;25:208-14.
3. Cammisuli DM, Cammisuli SM, Fusi J, Franzoni F, Pruneti C. Parkinson's Disease-Mild Cognitive Impairment (PD-MCI): A Useful Summary of Update Knowledge. *Front Aging Neurosci*. 2019;11:303.
4. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord*. 2007;22:1689-707.
5. Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Mov Disord*. 2008;23:837-44.
6. Yarnall AJ, Breen DP, Duncan GW, et al. Characterizing mild cognitive impairment in incident Parkinson disease: The ICICLE-PD Study. *Neurology*. 2014;82:308-16.
7. Williams-Gray CH, Evans JR, Goris A, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. *Brain*. 2009;132:2958-69.

# MDS Virtual Congress 2020: Highlights from 2020 - Looking Toward 2021

## Highlights from 2019-2020 Clinical Studies: Other Movement Disorders

— *Orlando Barsottini MD, PhD, Professor of Neurology, Federal University of São Paulo, Brazil*

Important clinical studies were published in the past year focusing on abnormal involuntary movements across different disease areas including ataxias, autoimmune diseases, dystonias and choreas. On the topic of ataxias, in an article entitled "Biallelic expansions of an intronic repeat in ***RFC1*** is a common cause of late-onset ataxia" (Nature Genetics, 2019), Cortese et al. demonstrated that biallelic intronic AAGGG repeat expansions in the replication factor C subunit 1 (RFC1) gene is a common cause of late-onset ataxia, especially in CANVAS phenotype—cerebellar ataxia, neuropathy and vestibular areflexia—and with an expansion carrier frequency of 0.7% in Europeans. Another study of the prevalence of ***RFC1*** gene in North America (Syriani et al., "Prevalence of RFC1-mediated spinocerebellar ataxia in a North American ataxia cohort," published in Neurology Genetics 2020) evaluated a cohort of 596 adult-onset patients with undiagnosed familial and sporadic ataxia and identified 29 patients with mutation in ***RFC1*** (3.2%). The most common phenotype consisted of ataxia and neuropathy (48%) and a complete CANVAS phenotype was seen in only 28%.

Matozzi et al. study, "Hashimoto encephalopathy in the 21st century," published in Neurology 2020, evaluated whether pretreatment diagnosis of Hashimoto encephalopathy (HE) can predict response to steroids. Twenty-four patients diagnosed with HE pretreatment were evaluated; only 31.6% responded to steroids. They concluded that pretreatment diagnosis of HE does not predict steroid responsiveness and that this syndrome may need redefinition. Furthermore, a new antibody (IgG) specific for kelch-like protein 11 was identified in patients with seminoma-associated paraneoplastic encephalitis. In a 2019 article published in The New England Journal of Medicine, Mandel-Brehm et al. described 13 patients with seminoma or testicular microlithiasis associated with ataxia, vertigo and diplopia. It is noteworthy that conventional paraneoplastic antibodies associated with seminoma, including Ma2 IgG, were not detected in these patients.

The study entitled "Risk of spread in adult-onset isolated focal dystonia: A prospective international cohort study" by Berman et al. (*Journal of Neurology, Neurosurgery, and Psychiatry*, 2020) prospectively evaluated the risk of spread of focal dystonia. These authors evaluated 487 patients with isolated dystonia affecting only upper face, neck, larynx and hand and found that disease spread occurred in 50% of the patients with blepharospasm, 8% with cervical dystonia, 17% with hand dystonia and 16% with laryngeal dystonia. Increased spread risk was associated with a positive family history and self-reported alcohol responsiveness.

In "The clinical features and progression of late-onset versus younger-onset in an adult cohort of Huntington´s disease patients" (*Journal of Huntington's Disease*, 2020) Anil et al. compared clinical features of late-onset (>70 years) and young-onset (<30 years) Huntington's disease (HD) patients. At first clinical presentation, both groups presented with the same UHDRS scores. The late-onset group had higher chorea scores and the young-onset group had more dystonia and eye movements, a greater rate of motor progression (especially bulbar) and bradykinesia. These authors concluded that phenotypic differences were found in terms of initial presentation and rate of motor progression with likely implications for therapeutic trials involving HD patients of different ages.

**References:**


1. Cortese A, Simone R, Sullivan R, Vandrovcova J, Tariq H et al. Biallelic expansions of an intronic repeat in ***RFC1*** is a common cause of late-onset ataxia. Nat Genet. 2019 Apr;51(4):649-658
2. Dona Aboud Syriani , Darice Wong , Sameer Andani, Claudio M De Gusmao, Yuanming Mao et al. Prevalence of RFC1-mediated spinocerebellar ataxia in a North American ataxia cohort. Neurol Genet 2020 May 20; 6(3): e440
3. Matozzi S, Sabater L, Escudero D, Ariño H, Armangue T et al. Hashimoto encephalopathy in the 21st century. Neurology. 2020 Jan 14;94(2):e217-e224
4. Mandel-Brehm C, Dubey D, Kryzer TJ, O'Donovan BD, Tran B et al. Kelch-Like protein 11 antibodies in seminoma-associated paraneoplastic encephalitis. N Engl J Med. 2019 Jul 4;381(1):47-54
5. Brian D Berman, Christopher L Groth , Stefan H Sillau, Sarah Pirio Richardson , Scott A Norris et al. Risk of spread in adult-onset isolated focal dystonia: A prospective international cohort study. J Neurol Neurosurg Psychiatry 2020 Mar;91(3):314-320
6. Megha Anil, Sarah L Mason, Roger A Barker. The clinical features and progression of late-onset versus younger-onset in an adult cohort of Huntington´s disease patients. J Huntingtons Dis. 2020; 9(3):275-282


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# Highlights from 2019-2020 Clinical Studies: Parkinson's Disease

*— Shen-Yang Lim, MD, FRACP, FASc, Professor of Neurology, University of Malaya, Kuala Lumpur, Malaysia*

This plenary lecture reviewed high-impact studies in PD published since the Sept 2019 MDS International Congress in Nice, France, and highlighted ongoing trials with anticipated completion in 2020/2021. Studies were mostly Phase 2 (proof of concept) or Phase 3 clinical trials (i.e., with efficacy data), with an emphasis on disease-modifying therapies (DMTs).

McFarthing et al. raised awareness of the clinical trial landscape in PD by reviewing the ClinicalTrials.gov database (≈2,500 trials in PD registered as of 01/2020, since its launch in 2000).[1] They found 145 active Phase 1-3 trials of drug therapeutics, 61% of which focused on symptomatic therapies (2/3 for motor and 1/3 for non-motor symptoms [NMS]) and 39% for DMTs.

Olanow et al. reported a positive RCT of sublingual apomorphine as a rescue treatment for OFF periods;[2] this has subsequently been FDA-approved. Subcutaneously-administered levodopa (less invasive vs. the intra-jejunal route) is also being tested in Phase 3 trials, with expected completion in 2021 (NCT04006210; NCT04380142). A major problem, however, is that infusion treatments remain beyond the reach of the vast majority of PD patients worldwide.[3]

In the non-motor sphere, Peball et al. used an "enriched enrolment randomized withdrawal (EERW)" design to show that nabilone (a synthetic cannabinoid) reduced NMS burden (especially anxiety, insomnia and possibly pain).[4] Although well tolerated overall, further study of the long-term effects of therapeutic cannabinoid use is needed. The beneficial role of probiotics as a treatment for constipation was highlighted.[5,6] In PD-related dementia, results are awaited for an RCT using a D1-dopamine agonist involved in cognition (NCT03305809).

One-third of ongoing clinical trials in PD are testing repurposed drugs,[1] including GLP-1 (glucagon-like peptide 1) agonists "borrowed" from the diabetes field. There are currently 8 ongoing trials of GLP-1 agonists, including a study of exenatide ER weekly-subcutaneous injections over 2 years (NCT04232969). The "Linked Clinical Trials (LCT)" initiative has spearheaded multiple drug repurposing efforts in PD.[7]

Unfortunately, despite initial promise, the Parkinson Study Group documented no benefits of nilotinib (6 months treatment)[8] or isradipine (3 years).[9] Another c-Abl tyrosine kinase inhibitor with blood-brain barrier penetration, K0706, is undergoing phase 2 testing; studies are estimated to be completed in 2021 (NCT03655236; NCT03996460).

Passive immunization using monoclonal antibodies targeting extra-cellular α-synuclein was studied, with results awaiting full publication[10] (industry announcements suggested that although "PASADENA did not meet its primary objective, it did show … signals of efficacy on multiple prespecified secondary and exploratory clinical endpoints ... and was generally well-tolerated". A study of a similar agent, Cinpanemab, is expected to conclude in 2021 (NCT03318523).

A recent proof-of-concept study demonstrated that enhancing glycolysis using terazosin and related compounds attenuated PD progression in animal and cellular models; the authors also found evidence from human databases showing slower disease progression, decreased PD-related complications, and a reduced frequency of PD diagnosis in individuals taking these agents.[11] However, interventional research in patients is still very preliminary (NCT03905811).

Personalized therapies for genetically-defined PD have entered clinical trials. High-dose ambroxol demonstrated target engagement in a Phase 2 study;[12] a study in demented patients is expected to be completed in 2021 (NCT02914366). Another GBA-directed therapy, Venglustat, is also being tested in a large Phase 2 study (NCT02906020). In a Phase 1b study, the LRRK2 kinase inhibitor DNL201 (NCT03710707) was reported by industry to have "met all biomarker goals".[13] A larger question is whether these drugs will be useful "only" for mutation carriers, or could they also benefit the much larger group of "idiopathic" PD patients?[14,15] (note that lysosomal glucocerebrosidase activity is reduced also in the brains of idiopathic patients; similarly, LRRK2 kinase activity is increased in PD patients with - and *without* - LRRK2 variants).[14,16-18]

The lecture concluded that significant advancements in understanding the biology underlying PD are now reflected in a wide range of DMT trials; the breadth of this therapeutics pipeline is encouraging.[1]

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MDS Virtual Congress 2020: Highlights from 2020 - Looking Toward 2021, *continued from p. 11*

**References**


1. McFarthing K, Buff S, Rafaloff G, Dominey T, Wyse RK, Stott SRW. Parkinson's disease drug therapies in the clinical trial pipeline: 2020. *J Parkinsons Dis*. 2020;10(3):757-774.
2. Olanow CW, Factor SA, Espay AJ, et al. Apomorphine sublingual film for off episodes in Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Neurol*. 2020;19(2):135-144.
3. Lim SY, Tan AH, Ahmad-Annuar A, et al. Parkinson's disease in the Western Pacific Region. *Lancet Neurol*. 2019;18(9):865-879.
4. Peball M, Krismer F, Knaus HG, et al. Non-motor symptoms in Parkinson's disease are reduced by nabilone. *Ann Neurol*. 2020;88(4):712-722.
5. Tan AH, Lim SY, Chong KK, et al. Probiotics for constipation in Parkinson's disease: A randomized placebo-controlled study. *Neurology*. 2020 Oct 12:10.1212/WNL.0000000000010998. doi: 10.1212/WNL.0000000000010998. Epub ahead of print.
6. Tan AH, Hor JW, Chong CW, Lim SY. Probiotics for Parkinson's disease: Current evidence and future directions. *J Gastroenterol Hepatol Open*. First published: 20 November 2020. doi.org/10.1002/jgh3.12450
7. Brundin P, Wyse RK. The Linked Clinical Trials initiative (LCT) for Parkinson's disease. *Eur J Neurosci*. 2019;49(3):307-315.
8. Simuni T, Fiske B, Merchant K, et al. Nilotinib in patients with advanced Parkinson's disease: A randomized phase 2A study (NILO-PD). *medRxiv* 2020.05.11.20093146; doi: https://doi.org/10.1101/2020.05.11.20093146.
9. Parkinson Study Group STEADY-PD III Investigators. Isradipine versus placebo in early Parkinson disease: A randomized trial. *Ann Intern Med*. 2020 5;172(9):591-598.
10. Chatterjee D, Kordower JH. Immunotherapy in Parkinson's disease: Current status and future directions. *Neurobiol Dis*. 2019;132:104587.
11. Cai R, Zhang Y, Simmering JE, et al. Enhancing glycolysis attenuates Parkinson's disease progression in models and clinical databases. *J Clin Invest*. 2019;129(10):4539-4549.
12. Mullin S, Smith L, Lee K, et al. Ambroxol for the treatment of patients with Parkinson disease with and without glucocerebrosidase gene mutations: A nonrandomized, noncontrolled trial. *JAMA Neurol*. 2020;77(4):427-434.
13. https://www.globenewswire.com/news-release/2020/01/14/1970308/0/en/Denali-Therapeutics-Announces-Broad-Pipeline-Progress-Including-Positive-Results-From-Its-LRRK2-Program-for-Parkinson-s-Disease.html; accessed 9 August 2020.
14. Schneider SA, Alcalay RN. Precision medicine in Parkinson's disease: emerging treatments for genetic Parkinson's disease. *J Neurol*. 2020;267(3):860-869.
15. Espay AJ, Kalia LV, Gan-Or Z, et al. Disease modification and biomarker development in Parkinson disease: Revision or reconstruction? *Neurology*. 2020;94(11):481-494.
16. Alessi DR, Sammler E. LRRK2 kinase in Parkinson's disease. *Science*. 2018;360(6384):36-37.
17. Di Maio R, Hoffman EK, Rocha EM, et al. LRRK2 activation in idiopathic Parkinson's disease. *Sci Transl Med*. 2018;10(451):eaar5429.
18. Tolosa E, Vila M, Klein C, Rascol O. LRRK2 in Parkinson disease: challenges of clinical trials. *Nat Rev Neurol*. 2020;16(2):97-107.

# Digital Health –Not a Mirror to the Analog World But a Patient-Up Redesign

— *Alberto Espay, MD, MSc, Professor of Neurology, University of Cincinnati, Cincinnati, OH, USA; Co-Chair, MDS Task Force on Technology*
— *Walter Maetzler, MD, Senior Consultant, University Hospital Schleswig-Holstein, Kiel, Germany; Co-Chair, MDS Task Force on Technology*


*Alberto Espay, MD, MSc*


*Walter Maetzler, MD*

At the Plenary Session, "Digital Health Technologies in Movement Disorders," held during the MDS Virtual Congress on September 16, 2020, along with our colleague Bas Bloem, we shared the virtual podium to discuss how to materialize the promise of Digital Health. Must available technologies be adapted to patients or new technologies developed based on their needs? The current model suggests we can make do with what we already have. However, the developmental pathway ahead, if technologies are to have a longer shelf life and become the center of the health universe, is to start from defining what is most important to the individual patients and then determine the type and mode by which technologies can be developed and deployed with versatility to satisfy those needs.

Several major obstacles have been identified in the path to harnessing the promise of technology for healthcare. The first is the determination of the appropriate number of "sensory channels" necessary to capture information relevant to the wearer. The next is to define what we will accept as "validation". If validation requires a correlation with a previously developed clinical scale or questionnaire, then we would in fact be just "digitizing" them rather than entirely revisiting clinical categories from a patient's perspective.

A major tension was highlighted at the meeting. How can the same "personalized and integrated care" system satisfy both individual and population needs? To satisfy an individual need, a technology must provide indispensable information to the individual using it –and may be irrelevant to anyone else in the same population. The adherence to a technology by individual patients allows their data to increase in value in the long term. But how can that individualized data also be used more globally? How might become endpoints in clinical trials, contribute to regulatory approvals, identify at risk populations, and inform the allocation of medical resources?

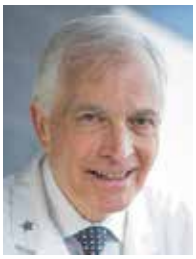
Enter Metadata. Metadata refers to the data that accompany and describe the primary data to better understand the context in which it was obtained, and assist in data management, data sharing, and data analysis. Metadata, in essence, is the bridge that gaps three ostensibly disparate goals in data collection: the data are accurate and interpretable, the information is relevant to patients, and the information is acceptable as outcomes for regulatory agencies. Metadata, in sum, is the mechanism to validate the same data for the individual and for the population.

An upcoming testing ground for the power of patient-centric and population-valid digital health pathway will be the development of an MDS e-Diary for patients with Parkinson's disease. A diary can be thought of as the most individualized source of data (the paper versions of it under use are instead multiple-choice clinical questions repeated every half hour throughout as many days patients can answer them). If digital technologies can capture data in the naturalistic environment in which diaries are typically conceived and executed, the output can demonstrate that technology may not just become a replacement of the paper world but a veritable form of Digital Health, re-designed "from the patient up".

# MDS Video Challenge: Messages from the Co-Masters of Ceremony

## "I Have Come to Praise Sethi, Not to Bury Him!"

*— Anthony Lang, OC, MD, FRCPC, Director, Movement Disorders Clinic, Toronto Western Hospital, Toronto, ON, Canada*



The 2020 MDS Video Challenge (VC) saw some unexpected developments, some good and some not so good. In moving to a virtual format, we were able to reach a much larger audience than in the past, we involved a greater number of outstanding Experts than ever before in the case discussions (the "All Stars" from past years) and we provided a revised approach to the case presentations that many felt enhanced their educational value. We missed the excitement of the live format with the opportunity to see Experts "thinking on their feet" and being challenged in real time to discuss the phenomenology and differential diagnosis. We also missed the more relaxed and entertaining live interchange between the Masters of Ceremony and between them and the Experts that the audience routinely enjoys and is one of the components of the "special sauce" that has made the VC so popular over the years. Another "not so good" unexpected development of this year's VC was the announcement by Dr. Kapil Sethi that 2020 would be his last year serving as co-Masters of Ceremony.


I first proposed idea of the "Video Olympics" to the MDS Congress Scientific Program Committee (CSPC) about 14 years ago. A brief history of the event is in the Preface to the September 2020 supplement of *Movement Disorders Clinical Practice*, which contains the cases presented at the 2019 Nice International Congress. The Preface does not mention that when the idea developed, Kapil Sethi was a natural selection for my "partner in crime". Although Kapil was a good friend and colleague, that played only a small role in his selection. I knew that he was the remarkable workhorse behind the massive success of Neurobowl at the annual meeting of the American Academy of Neurology (AAN). His knowledge base, not only in Movement Disorders but also in general neurology, is prodigious. He is dedicated to the careful deconstruction of movement disorders cases starting with a critical assessment of the phenomenology. His memory of cases he has come across in the past is also quite legendary. He regularly humbly admits that he is one of the few "experts" who didn't actually receive formal training in Movement Disorders but learned this starting at the feet of the fathers of the field by attending the "Unusual Movement Disorders" sessions at the AAN (one of the inspirations of the VC), chaired by Stan Fahn and David Marsden.


MDS Video Challenge: Messages from the Co-Masters of Ceremony, *continued on p. 15*

MDS Video Challenge: Messages from the Co-Masters of Ceremony, *continued from p. 14*

Finally, our friendship inspired the chemistry that I believe has been an important reason for the success of the annual event.

Following the Nice International Congress, Kapil informed me that the 2020 meeting was probably going to be his last. He is looking forward to reducing his workload (and believe me, the time we spend preparing the VC is infinitely more than we spend on any other academic exercise) and having more time for his family. Further, he has been plagued with chronic back problems – the audience was not aware of the discomfort he was in as his "Doc" hobblingly tried to match my Marty McFly's run into

the ballroom in our "Back to the Future" entrance at the 10th anniversary of the VC in 2017 in Vancouver. When we learned that the 2020 VC was to be virtual, I got him to agree to delay his retirement announcement until we could do this event live again. However, when we came to the end of recording the last case for the 2020 virtual event, he sprang it on me (and the others participating in the recording session). Keeping this a secret was even harder than you might expect, since we weren't recording cases in the order that they were going to be shown and we still had quite a few more to complete at that point. The virtual format presented us some new and important challenges and the time we spent preparing the cases was considerably more than in past years. This created a certain amount of tension and stress and I really believe that my obsessive nature probably ended up driving him crazy and might have contributed to his final decision.

Whatever his exact reason was, this end of our very successful "run" was inevitable. Both of us hope that the VC will remain a part of the International Congress long after the two of us both leave the podium. The changes we implemented this past year will likely result in further organizational changes for 2021 and with Kapil Sethi's announcement, we will need to revise the roles and positions of the Masters of Ceremony. As Kapil has repeatedly reminded me, "No one is irreplaceable". However, his contribution to the Society and to the general field of Movement Disorders in his role as a Master of Ceremony of the VC has been immense and its impact will be felt "Far into the Future". Thanks for everything, Doc!

## Farewell to the Video "Olympics"

*— Kapil Sethi, MD, FRCP, Professor Emeritus, Augusta University, Augusta, GA, USA*

In 2007, during a meeting of the CSPC in the "La Defense" area of Paris, Tony proposed his brilliant idea of holding a "Video Olympics" along the lines of the well-known Olympics. The Chairman of the committee at that time, Serge Przedborski, thought that I might be a good co-host given my long experience with Neurobowl at the AAN. I "accidently" missed this meeting as I had gone to watch the final laps of Tour de France at the Avenue des Champs-Élysées so I learned of the fact that I was "volunteered" upon my return. I accepted readily, knowing that this way I wouldn't have to be on the Panel of Experts discussing the cases during the live meeting!

The Video Olympics/Games/Challenge soon became the educational highlight of the year for me. Over 13 years, I have learned more from

Integrated and Patient-Centered Management of Parkinson's Disease, *continued on p. 16*

MDS Video Challenge: Messages from the Co-Masters of Ceremony, *continued from p. 15*

organizing this event with Tony than from anything else. Meeting with the bright young minds to help prepare and present the cases has been inspirational and several of them have participated on the Panel of Experts in the following years.

The most difficult part was to get Tony to wear a tuxedo (sometimes ironed properly) and to keep up with the hypo-manic speed of that man that I admire.

I will miss interacting with the outstanding faculty whose knowledge and dedication was exemplary. I will miss organizing the event with Tony. I will not miss trying to limit the number of cases and frantically trying to keep everyone on time.

As of now, I am getting used to being old.

*Kapil Sethi and Anthony Lang (front) at the first MDS Video Olympics, during the International Congress in Chicago, IL, USA, in 2008.*

# 30 Years of "The Aspen Course": A Comprehensive Review of Movement Disorders for the Clinical Practitioner

— *Joseph Jankovic, MD, Professor of Neurology, Distinguished Chair in Movement Disorders, Director, Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, TX, USA*

During the course of our planning and developing The Movement Disorder Society, now the International Parkinson and Movement Disorder Society (MDS), Stan Fahn, David Marsden, and myself, the first, second and third presidents of the Society, had many discussions about the need to develop a comprehensive course on movement disorders. We considered various potential venues and finally we settled on Aspen, CO, USA. This decision was partly stimulated by the invitation to participate at the 9th Annual Symposium on Medical Problems of Musicians and Dancers, in the Wheeler Opera House, sponsored by The Cleveland Clinic Foundation and the Aspen Music Festival, held in Aspen in early August, 1991. The three of us thought that this would be a good opportunity to inaugurate the course, "A Comprehensive Review of Movement Disorders for the Clinical Practitioner", which has since been called simply as "The Aspen Course". At that time, none of us had predicted that the course would gradually grow into one of the most popular and prestigious courses on movement disorders.

The first course was held August 5-7, 1991, at the stately ballroom of the legendary Hotel Jerome (Figures 1 and 2). This was the venue for the course until 2011 when the Hotel Jerome was not large enough to accommodate the growing number of attendees and the course moved to the St. Regis Hotel, which had remained the venue for the summer course until and including 2019. Unfortunately, in 2020, because of the COVID-19 pandemic, the 30th anniversary course was virtual.

Aspen clearly was a superb choice for the course venue, not only because of the exclusive hotel accommodations, as well as other more affordable housing, but also because it was a perfect destination for combining work and pleasure. In addition to the splendid ambience and beauty of Aspen and its surrounding areas, Aspen offers the world renowned Aspen Music Festival, Aspen Opera, Aspen Institute and many other amenities,

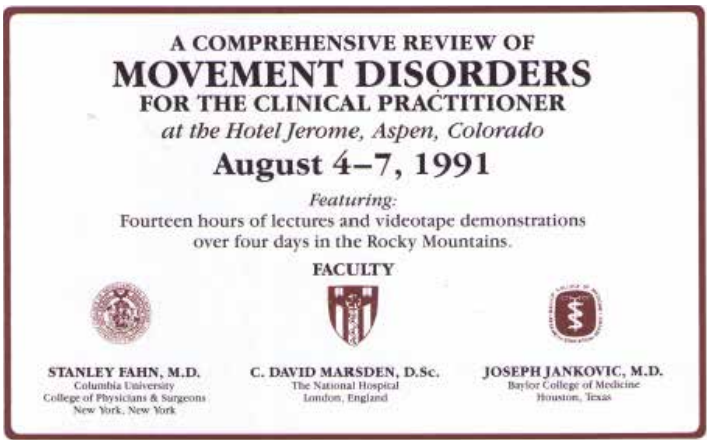

A COMPREHENSIVE REVIEW OF
MOVEMENT DISORDERS
FOR THE CLINICAL PRACTITIONER
*at the Hotel Jerome, Aspen, Colorado*
August 4–7, 1991
*Featuring:*
Fourteen hours of lectures and videotape demonstrations over four days in the Rocky Mountains.
FACULTY
STANLEY FAHN, M.D. Columbia University College of Physicians & Surgeons New York, New York
C. DAVID MARSDEN, D.Sc. The National Hospital London, England
JOSEPH JANKOVIC, M.D. Baylor College of Medicine Houston, Texas

*Figure 1: Announcement of the first "Aspen course"*

*Figure 2: From left to right: Stan Fahn, MD; Joseph Jankovic, MD, C. David Marsden, MD during the first Aspen course in 1991*

including first-class dining, galleries, and museums. Many things have been said to exalt the virtues of Aspen: "summer camp for your brain", "aphrodisiac for the soul", "the mountain capital of culture", "heaven on earth", and "when God closed the Garden of Eden, God opened Aspen". During the 20th anniversary celebration of the course, a banner was posted across the Main Street (Figure 3), and Mayor Steven Skadron came to congratulate us and thank us for bringing $1 million to the Aspen economy each year.

The original primary goal of the course was to provide the most current and comprehensive information about Parkinson's disease, other parkinsonian disorders and all hyperkinetic disorders including tremor, dystonia, chorea, athetosis, ballism, tics, myoclonus, stereotypies, drug-induced movement disorders, gait disorders, ataxias, and paroxysmal, autoimmune, and functional (psychogenic) movement disorders and other disorders of movement and their medical and surgical treatments. The didactic lectures, which included introductory reviews of phenomenology and basal ganglia anatomy and physiology, were richly supplemented by videos as the emphasis was on classic and nuanced phenomenology. This traditional educational program was markedly enhanced by active inter-personal interactions between participants and faculty during Q&A sessions after each lecture, coffee breaks, and informal discussions in the lobby, pool side, bars, restaurants, bike rides and hikes. Finally, video rounds, accompanied by food, popcorn, wine and beer, usually held the 3rd night of the course, became one of the most anticipated and popular sessions. During these nights at the movie the participants had an opportunity to present videos of their challenging cases for discussion by the faculty and other attendees.

30 Years of "The Aspen Course": A Comprehensive Review of Movement Disorders for the Clinical Practitioner, *continued on p. 18*

30 Years of "The Aspen Course": A Comprehensive Review of Movement Disorders for the Clinical Practitioner, *continued from p. 17*

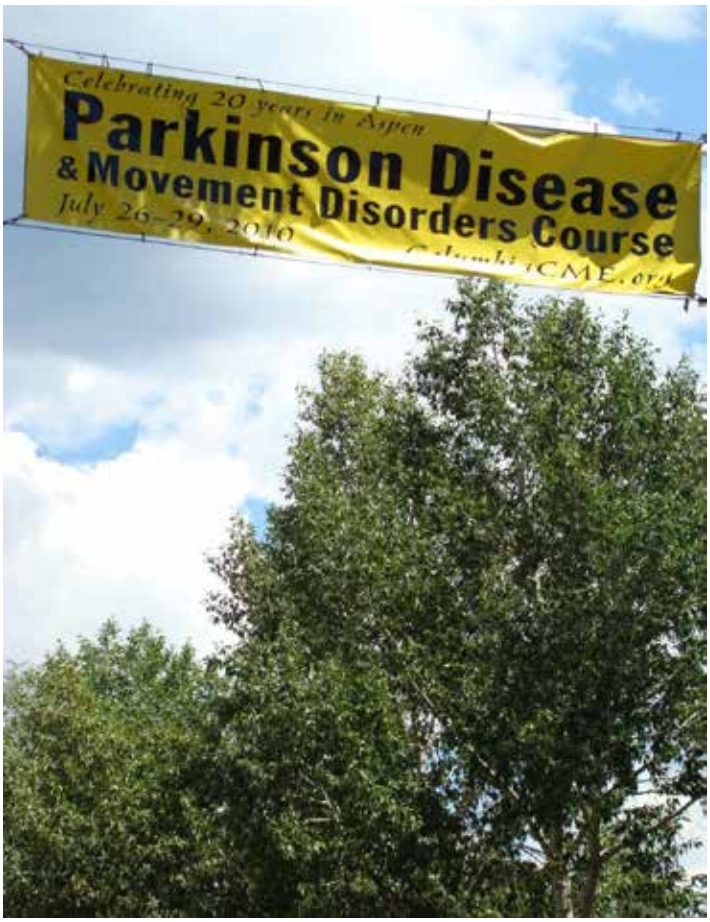



*Figure 3: Banner across Main street, Aspen, drawing attention to the 20th anniversary of the Aspen course*

Besides the satisfaction of delivering valuable educational program, I have always looked forward to the annual Aspen course as a rendezvous with my co-faculty who also happen to be my close personal friends. I fondly recall our daily lunches and dinners with David Marsden and Stan Fahn during which we discussed not only topics related to movement disorders, but also debated views on international politics, and shared personal experiences and philosophies. Our annual dinners at Pinons will be always remembered for the lively conversations supplemented with David's expert opinions on particular wines. David was known to all of us as a "connoisseur of good living". My children referred to him as "James Bond", not only because of his distinctive English accent but also because of his irresistible charm and good looks (Figure 4). Unfortunately, David suddenly died on Erev Yom Kippur, September 29, 1998, not from liver or lung disease (he was an avid consumer of wine and cigarettes), but from a genetic congenital heart defect. After David's untimely death at the young age of 60, Stan and I invited Mark Hallett, MD and Peter Jenner, PhD, students and colleagues of David, to join us between 1999 and 2008 as co-faculty (Figure 5). Subsequently, between 2009 and 2015, the faculty consisted of Drs. Fahn, Hallett, and Jankovic. After 25 years of affiliation with Columbia University, that provided CME accreditation for the course from the beginning, the faculty decided to transition the course to MDS, which has been the CME provider and organizer since 2016.

The enduring course materials gradually evolved from a one-volume syllabus, to 3-volume syllabus, to flash drive, and, finally, web-based slides (Figure 6). Inspired by the Aspen course, two editions of the book, *"Principles and Practice of Movement Disorders"*, have been published by Elsevier, in 2007 (Fahn and Jankovic) and 2011 (Fahn, Jankovic, Hallett) (Figure 7), respectively. We hope that by the time of the 2021 course, probably a hybrid format (virtual and in-person), the third edition (Jankovic, Hallett, Okun, Comella, Fahn) will be published.

Although over the years since 1991 the faculty changed, except for Drs. Fahn and Jankovic (Figures 8-9), the aim of the course remained the

*Figure 4: C. David Marsden (1938-1998) from Preface to Fahn S, Jankovic J, Hallett M. Principles and Practice of Movement Disorders, Churchill Livingstone, Elsevier, Philadelphia, PA, 2011:1-548 .*

30 Years of "The Aspen Course": A Comprehensive Review of Movement Disorders for the Clinical Practitioner, *continued on p. 19*

30 Years of "The Aspen Course": A Comprehensive Review of Movement Disorders for the Clinical Practitioner, *continued from p. 18*

*Figure 5: Aspen faculty between 1999 and 2008. From left to right: Peter Jenner, PhD, Joseph Jankovic, MD, Stan Fahn, MD, Mark Hallett, MD*

same: to provide the most comprehensive and up-to-date information about the basic and clinical science of movement disorders. In 2020, the 30th anniversary course, as many other meetings around the world, was virtual (Figure 10). The Virtual Aspen Course included seven faculty: Cynthia Comella, Stanley Fahn, Jennifer Goldman, Mark Hallett, Joseph Jankovic, Michael Okun, and Kapil Sethi. Additionally, three international guest panelists, Kailash Bhatia, Victor Fung, and Marie Vidailhet, joined the faculty for the video rounds session where participant videos were presented. As a result of the additional faculty, The Aspen Course is now more diverse and global. With the international platform and audience, 1,787 attendees registered for the virtual course, representing 86 countries. A comprehensive 28 lectures were recorded, highlighting the expanding knowledge in the field of Parkinson's disease, hyperkinetic movement disorders, and other movement disorders. While lectures were available on demand, the course also held five interactive sessions

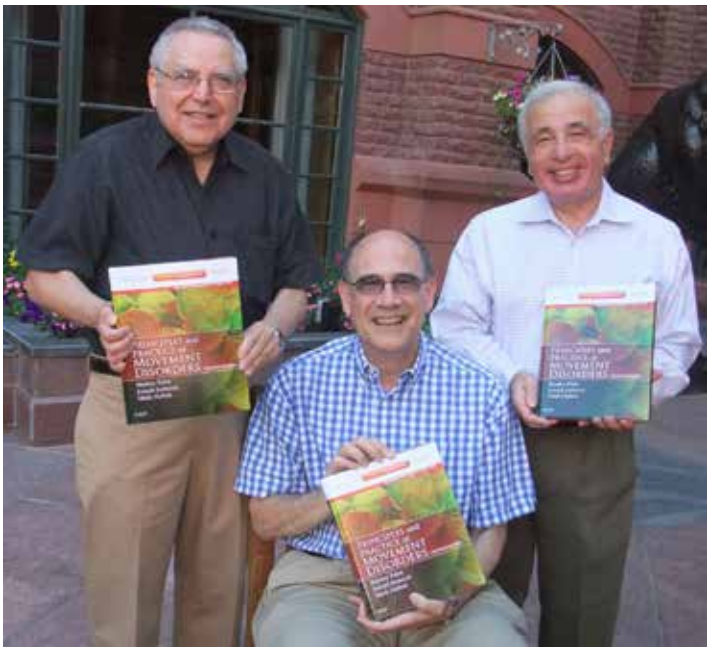


*Figure 7: Aspen faculty 2012: From left to right Stan Fahn, MD, Mark Hallett, MD, Joseph Jankovic, MD holding the 2nd edition of the "Aspen book".*

inclusive of scientific Q&A sessions, video rounds, and a discussion on career development and mentorship. Each session had consistent interaction and attendance ranged from 203 – 676 participants, which represents a marked increase from the usual 200 in-person participants in the prior courses (Figures 8-12).

Although the Aspen course was originally aimed at clinical practitioners, it rapidly expanded with focus on movement disorders fellows, who now constitute about 70% of all the participants. During the past five years, Dr. Okun, the course co-director (along with Dr. Comella), has often stated: "As a right of passage every movement disorders fellow must pass through the Aspen Course."

*Figure 6: 1 volume per year 1991-2003; 2 volumes 2004-2006; 3 volumes 2007-2011 (followed by flash drives/Web, 2012-2013 and Web ≥2014)*

30 Years of "The Aspen Course": A Comprehensive Review of Movement Disorders for the Clinical Practitioner, *continued on p. 20*

30 Years of "The Aspen Course": A Comprehensive Review of Movement Disorders for the Clinical Practitioner, *continued from p. 19*

*Figure 8: Faculty Aspen Course 2019. From left to right: Michael Okun, MD, Jennifer Goldman, MD, Kapil Sethi, MD, Cynthia Comella, MD, Stan Fahn, MD, Joseph Jankovic, MD, Mark Hallett, MD*

## Acknowledgement:

I want to express my deep gratitude to all the sponsors who have generously supported the Aspen course over the years and to all CME coordinators who have guided us through the 30-year journey and helped contribute to the success of the course. These include Mohamed Ali and Laura Yasso of Columbia University CME, as well as Annette Schott and Kate Rudolph at the MDS International Secretariat.

*Figure 9: Fellows, Aspen Course 2019*


*Figure 10: Virtual Aspen Course 2020*

# The New MDS Basic Science Special Interest Group

— *Per Svenningson, MD, PhD, Professor of Neurology, Department of Clinical Neuroscience at the Karolinska Institutet, Department of Neurology at Karolinska University Hospital, Stockholm, Sweden; Chair, MDS Basic Science Special Interest Group*

The MDS Basic Science Special Interest Group (SIG) was recently established and had its first meeting on September 8, 2020. The Basic Science SIG represents research-oriented neurologists and neuroscientists with interest in fundamental mechanisms underlying Movement Disorders. An important goal for us is to update clinical neurologists and neuroscientists on the forefront of research related to genetics, imaging, preclinical models and pathophysiological mechanisms of Movement Disorders and their therapies. We aim at developing educational programs, online materials and to survey interest in Basic Science of MDS members.

We were very pleased to learn that the Young Members Group had recently performed a survey on what basic scientists expect from MDS and how MDS can facilitate interactions between clinicans and basic scientists. This timely survey reached the full spectrum from undergraduate students to principal investigators. It shows a need for increased collaboration and interactions between preclinical and clinical scientists on various Movement Disorders topics.

The Basic Science SIG is encouraged by this need and will try to tackle the task in several ways. We are developing a program where clinical residents and basic science trainees (PhD students and postdocs) are granted funding to collaborate on a scientific topic of shared interest. Each project will be supervised by a senior MDS-ES Mentor. Another initiative we are proposing is to include "Meet the professor" sessions at international and regional MDS congresses. This interactive format will be adopted from other conferences (e.g. AD/PD). The professor to meet is a senior person with a certain expertise and the interested participants sign up for such a session when they preregister for a meeting. "Meet the professor" sessions will allow face-to-face meetings in smaller group for discussion on career tips or on how to conduct research in a pre-specified area of Movement Disorders. We will also try to increase the visibility and presence of Basic Science at the MDS International Congress by suggesting relevant topics for sessions and arrange guided poster tours during the meeting.

Another aim of the Basic Science SIG is to ensure that the ES, PAS and AOS regional sections are arranging Basic Science courses or summer schools on a yearly basis. The courses shall introduce, update and engage young neurologists and neuroscientists regarding research on Movement Disorders and promote translational research involving multidisciplinary approaches. The format may vary between the regions, but learned experiences and planning are done in close interactions in the Basic Science SIG. To the extent that it is possible, lectures will be video recorded and become available to a broader audience via the MDS webpage.

To educate younger members, we have started to prepare presentations on general scientific topics such as "how to write a scientific paper" and "how to make an oral presentation". These presentations will be found on the MDS webpage.

The newly formed Basic Science SIG is looking forward to interacting with the larger MDS community to facilitate collaboration between clinicans and basic scientists. A special emphasis is put on educating and promoting research on basic mechanisms underlying Movement Disorders to the next generation of physician-scientists. We are therefore particularly motivated to work in close collaboration with the Young Members Group in the future.

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The New MDS Basic Science Special Interest Group, *continued from p. 21*

# MDS Basic Scientists Survey 2020

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## Introduction

The Movement Disorders field is entering an exciting new era where we can hope that major advances in our understanding of the genetics, molecular biology and pathophysiology of movement disorders can lead to clinically significant breakthroughs.

One of the current goals of the International Parkinson and Movement Disorder Society (MDS) is to engage more basic scientists to benefit the development of innovative, novel therapies for patients. Therefore, the Young Members Group initiated an online Basic Scientists Survey comprised of 19 questions. The purpose of the survey was to paint a clearer picture of what basic scientists expect from MDS and how MDS can facilitate interactions between clinicans and basic scientists.

## Results

### Demographics

The survey was sent out to 631 MDS members that had indicated basic science as one of their areas of interest. A representative sample of 96 responses was received. Ninety percent (90%) of respondents are young members (younger than 40 years of age). Regional representation was well balanced with 30% each coming from the European section (ES) and the Panamerican section (PAS) with slightly smaller numbers from Africa and the Asian and Oceanic section (AOS).

More than 90% of respondents had an MD and/or PhD degree (of which 32% with a PhD and 14,58% MD-PhD degree). Twenty six percent (26%) had a master's degree.

Looking at their current position, we reached the full spectrum from undergraduate students to principal investigators (PIs). As expected, 80% of them work in an academic environment.

Most of the respondents are studying Parkinson's disease, both at a basic or a clinical level.

### Suggestions on the poster sessions at the MDS

A slight majority of respondents (only 54%) were happy with the poster sessions at MDS and the level of interaction. There is clearly room for improvement, as 15% are unsatisfied with the current setup of the poster sessions. Half of the respondents submitted suggestions for improvements. The lack of interaction with (senior) basic scientists and the underrepresentation of basic science is clearly seen as a hiatus.

Many useful suggestions were received that could help improve the poster sessions, ranging from guided poster tours, over more platform presentations of selected posters to poster prizes.

### Interaction between basic scientists and clinicians

There is an almost unanimous (97%) interest in joint meetings between clinicians and basic scientists. There is clearly a need to converge clinical expertise with preclinical research including systems neuroscience. Trainees would like to have more chances at informal interactions. There is a special request for meetings specifically aimed at networking and collaboration opportunities between members. Special interest groups have been a nice evolution in this regard, but there clearly is a need for more.

More than 50% of respondents support more basic science sessions at the MDS Congress, as well as more basic science teaching courses and focused meetings on different research topics.

Some respondents indicated that it would be a good thing if sessions would include both basic and clinical research to ensure a comprehensive approach to each topic.

Ninety eight percent (98%) of respondents expressed their willingness to join interactive panel discussions/master classes with the leaders in their field.

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**Education modules for basic scientists on the MDS website**

On the other side, only 75% of respondents were happy with the education modules for basic scientists on the MDS website.

Courses on advanced research methodologies and a tool consortium similar to the Michael J. Fox Foundation (MJFF) would be perceived as extremely helpful.

A demand for a basic movement disorders course for basic scientists to help target research questions at the big unmet needs in the field, testifies of the interest of basic scientists for the clinical implications of their research as well as for translational research.

Career building tips would also be greatly appreciated by young scientists.

**How to improve the basic scientist engagement within the MDS**

A large majority (76%) thinks MDS can engage basic scientists more by adding other formats to the MDS Congress and other MDS meetings like discussed previously.

A basic science newsletter was also suggested multiple times as a means to increase visibility for basic science in movement disorders.

Support for junior researchers and/or graduate students for attendance and conference registration (reduced registration fees, travel bursaries specifically for basic scientists, etc.) could also increase involvement of basic scientists.

## Conclusions

Our survey demonstrates there is clearly an interest from basic scientists to be more involved in MDS, as well as an interest from movement disorders specialists to hear more from basic science. The field could benefit from more intense interactions and collaborations.

A drawback can be that many initiatives and conferences exist already catering for basic scientists. It could be interesting to explore if and how collaborations are possible with the other large conferences such as the AD/PD-meeting and other large organizations such as the MJFF.

Based on all suggestions received we formulate practical ideas that if implemented could help increase engagement of basic scientists in MDS.

## Action points

There is a clear need for improvement of the poster sessions. Guided poster tours, more platform sessions and poster prizes could be helpful.

There is a clear demand for a bigger role for basic science in MDS and at the MDS meeting.

Travel bursaries and/or reduced registration fees for basic scientists could increase participation.

There is definitely an interest in more basic science sessions as well as joint meetings between basic scientists and clinicians.

A tools consortium would definitely be a big plus for basic scientists. MDS-supported exchange programs, especially grants for basic science projects between basic scientists and MDS expert clinicians and even postdoctoral grants and a basic science summer school could also help improve the standing of MDS in the basic science field.

# Personalized Medicine in Parkinson's Disease: Disease Modifying Therapies

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— *K. Ray Chaudhuri, MD, FRCP, DSc, Wohl Clinical Neuroscience Institute, King's College, London, United Kingdom*
— *Beomseok (BJ) Jeon, MD, PhD, Department of Neurology and Movement Disorder Center, College of Medicine, Seoul National University, Seoul, South Korea*

Margherita Fabbri and Jee-Young Lee, members of the ***Moving Along*** Editorial Board, reached out to global MDS experts to gain their insights in personalized medicine and the future of treatment for patients with Parkinson's disease.


*Angelo Antonini, MD, PhD*


*K. Ray Chaudhuri, MD, FRCP, DSc*


*Beomseok (BJ) Jeon, MD, PhD*

**What were the most important mistakes or reasons of failures of the previous trials on neuroprotective treatment for Parkinson's disease?**

**Antonini:** I think there are several reasons to consider: The main one is the inclusion of uncharacterized study population (Fast vs. slow progressor; severe vs. mild fluctuations, genetic vs. non-genetic). The assumption that "one antibody/one small molecule" fits all is not supported by clinical evidence showing significant variability in PD progression.

**Chaudhuri:** A. Late start, early or de novo motor Parkinson's in some PD patients may be preceded by a long prodromal period when neurodegeneration has started and it may be too late for neuroprotection.

B: A typical focus on motor outcomes without using validated, holistic non-motor scales and as such missing potential signals on non-motor outcomes which can also be a signal for neuroprotection (such as cognition, pain, sleep, fatigue).

C: A dopamine only "tunnel vision" approach when we have a syndromic condition (Parkinson's) with multiple neurotransmitter deficits.

D: Lack of enriching trial population using an endophenotype approach (clinical) or specifically ignoring the concept of clinical non-motor endophenotyping.

**Jeon:** There are MANY reasons, and one of them is that PD is not a single disease with multiple mechanisms contributing to the onset and progression. However, we try one molecule for one proposed mechanism, thus we are almost doomed to failure.

**Which phase of the disease would you think should be tackled to develop a neuroprotective treatment?**

**Antonini:** There are three key milestones in the disease that we could tackle:

A. The onset and progression of motor symptoms

B. The development of motor fluctuations in levodopa treated patients

C. The development of levodopa resistant symptoms namely dementia/ postural instability and falls

**Chaudhuri:** Enriched RBD cases where the likelihood of phenoconversion is within four to five years.

**Jeon:** It is logical to stop the progression in the early phase or even preclinical phase of PD.

**Please give us your opinion on how close we are to enable that, taking into account feasibility data and economic considerations.**

**Antonini:** Delaying the onset would require a biomarker not only to determine the risk (i.e., RBD, Hyposmia, depression etc.) but to identify when an "at risk individual" is close phenoconversion. Unfortunately, this is not feasible now so one would have to recruit a large number of subjects and hope in a sufficient number of events.

Slowing progression in early subjects can be assessed but it requires selection of an early but homogeneous cohort of "rapid progressors" where we know changes in progression can be detected in one to two years. This has not been the case in the two of the most recent immunotherapy studies.

B and C are feasible. Of course, the risk would be that we do not know if we can stop the disease from spreading after it has reached multiple brain areas. However, at least having clear and easy to identify endpoints would help adequately power the study. Inclusions of patients on treatment would facilitate recruitment and make the study closer to real life.

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**Chaudhuri:** Not all RBD cases phenoconvert to Parkinson's disease. There is an overlap with Lewy Body Dementia, Multiple System Atrophy as well as other neurodegenerative conditions with dementia. We need to have an "enriched" RBD cohort where the likelihood of conversion to PD is higher (possibly associated with idiopathic hyposmia and abnormal Datscan with or without other prodromal signs) and address clinically feasible trials at this stage. To obtain such a cohort, charities and researchers need to have a "joined up" approach and not work in their own research "silos". Single center or small collaborative studies are likely to have less external validity compared to large scale multi-country, collaborative efforts in a diverse patient population.

**Jeon:** Currently, there are many cohort studies especially with RBD trying to identify conversion into PD. Many biomarkers are being developed to "time" the phenoconversion. However, as PD is diverse not only in etiology but also in clinical phenotypes and progression, it will be necessary to test the hypothesis in a homogeneous group to see whether we really can modify the progression of PD. An example would be genetic PD.

### Which clinical elements would you consider as key factors to develop upcoming trials on neuroprotective treatments?

**Antonini:** Definition of responder rate (the number of subjects not deteriorating above a specific threshold), definition of a stopping rule namely defining non-responders or loss of response (this is critical if you use a treatment that has to be administered every month over the entire duration of the disease). Inclusion of functional measures related to ADL is also essential.

**Chaudhuri:** To catch PD as early as possible. In my view, enriched RBD cases, or those with idiopathic hyposmia associated with some other prodromal PD signs (constipation, abnormal colour vision, major depression) with an abnormal Datscan needs investigating. Joined up clinical trials would be essential and perhaps also including colleagues from ENT as well as Sleep medicine.

**Jeon:** Current clinical rating scales are very good but are often subjective. Thus, adding objective measurement tools and biomarkers such as DAT imaging should be included in the parameters.

### What is the most important feature that we should take into consideration in the treatment of PD?

**Antonini:** We must target patients' autonomy in ADL and QoL. The motor assessment will no longer be sufficient as we know that many other features contribute to functionality and well-being of our patients. Preventing cognitive decline, which is the best predictor of rapid progression.

**Chaudhuri:** One size does not fit all. Parkinson's treatment must be individualised based on clinical phenotype and patient preference.

**Jeon:** The most important feature is very individualized in each patient, and changes over time with response to therapy and disease progression. It is something we always have to discuss with the patients what they consider the most important, and what we can do for them. For example, a tremor may be very bothersome to the patient even though it is not functionally disabling. Deliberating surgical management, which is not risk-free would require the most individualized approach.

### How would you think we could apply the current knowledge of pharmacogenomics and precision medicine for designing future drug trials in PD?

**Antonini:** This is an essential aspect as we know now that knowledge of the underlying genetic background is essential to understand the pathogenetic mechanisms and is associated with different progression and mechanisms of degeneration.

**Chaudhuri:** Precision medicine can be successfully used in a minority of PD where GBA positive or LRRK2 positive cases can be targeted for specific pathway related therapies such as ambroxol or kinase inhibitors.

**Jeon:** There is a high hope that we will be able to rely on genetic information to predict the response to therapy, thus providing the right drug at the right dose at the right time. However, pharmacogenomics is just in its infancy, and big data cohort for genomic research is needed.

Personalized Medicine in Parkinson's Disease: Disease Modifying Therapies, *continued on p. 26*

Personalized Medicine in Parkinson's Disease: Disease Modifying Therapies, *continued from p. 25*

**As you know, personalized medicine application for PD patients would require enormous economic efforts, not always affordable, for many countries and health care systems. Which strategies would you suggest applying, from a global perspective, to overcome those shortcomings?**

**Antonini:** Identification of patients based on progression goes in this direction as also clear definition of stopping rules in case of lack of response. This will allow us to limit costs and make treatments available to many more patients. We should look at oncology where stratification and genotyping are routine now.

**Chaudhuri:** Personalized medicine is crucial for the overall health of PD patients, not just in developed countries but also in developing countries, given the endemic rise in number of PD cases globally. True personalized care needs to enable the circle of personalized medicine (see Titova and Chaudhuri, Mov Disord. 2017) and this is not expensive and we need to move away from a total reliance on guideline based "one size fits all" approach! Management needs specific attention to vital 5's of PD (bone health, visual health, mental health, personality and comorbidity) among other issues in every people with Parkinson's. Targeted personalized therapy should be based on clinical subtypes (avoid dopamine agonists in those with Park sleep and possibility of sleep events resembling narcolepsy, avoid anticholinergics in de novo PD with mild cognitive impairment, etc.) and in some groups, pharmacogenetics may be relevant (white versus back PD and levodopa effect), although pharmacogenetics is unlikely to play any specific effect at large apart from research. In a very small group of patients with known GBA or LRRK2 mutation, there may be a role of precision medicine using validated molecules (if shown to be effective in robust clinical trials).

**Jeon:** We have always taught that PD medication has to be individualized. Moreover, we are ready to modify our treatment plan based on the response. Thus, good clinicians are acting like AI. There may be more economical AI than affordable clinicians in future. Until then, we need to continue to educate more clinicians to be knowledgeable in PD therapy.

**How do you imagine the treatment of PD patients in 50-100 years?**

**Antonini:** Fifty to 100 years is a very long time and it is hard to imagine where science will lead us by then. I think in 10-20 years brain cell regeneration and replacement will be feasible… use of brain stimulation systems will allow to preserve regional connectivity for longer time and stimulate cell growth and function. Early detection of neurological conditions will be possible.

**Chaudhuri:** I would envisage treatment for Parkinson's in 50-100 years to have several; specific strands.

A. There will be a disease specific angle: with (a) use of validated neuroprotective molecules along with symptomatic therapy which will be motor and nonmotor stage orientated.
B. There will be personalised medicine therapy with level 1 evidence base guided management of key nonmotor symptoms (anxiety, pain, constipation, RBD, dementia for instance) for many of which currently there is no such evidence base. And precision medicine in selected gene positive cases (such as GBA positive PD).
C. We will use pharmacogenetics in selected cases to predict susceptibility to impulse control disorders, dyskinesias as well as to address ethnic disparities in drug responses.
D. There will be a "holistic" routine package to address the "vital 5" of Parkinson's: mental health, bone health, gut health, vison health and comorbidity.

**Jeon:** I will not answer because I will prove to be wrong.

**Additional References:**

Antonini A, Bravi D, Sandre M, Bubacco L. Immunization therapies for Parkinson's disease: state of the art and considerations for future clinical trials. Expert Opin Investig Drugs. 2020 Jul;29(7):685-695.

Titova N, Chaudhuri KR. Personalized medicine in Parkinson's disease: Time to be precise. Mov Disord. 2017 Aug;32(8):1147-1154.

Kim HJ, Jeon B. How close are we to individualized medicine for Parkinson's disease? Expert Rev Neurother. 2016 Jul;16(7):815-30.

Grimes D, Antonini A, Ferreira JJ, Sanchez-Ferro Á, Lynch T, Rascol O, Růžička E, Eggers C, Mestre TA. Patient-centred management of Parkinson's disease. Lancet Neurol. 2020 Nov;19(11):887-888

Marras, C., Chaudhuri, K.R., Titova, N. et al. Therapy of Parkinson's Disease Subtypes. Neurotherapeutics (2020). https://doi.org/10.1007/s13311-020-00894-7

Ray Chaudhuri K, Titova N. Societal burden and persisting unmet needs of Parkinson's Disease. European Neurological Review. 2019:14(1):28–35. Doi:10.17925/ENR.2019.14.1.28

Titova N, Chaudhuri KR. Personalized medicine in Parkinson's disease: Time to be precise. Mov Disord. 2017 Aug;32(8):1147-1154.

# Clinical Neurophysiology and Non-Invasive Brain Stimulation for Parkinson's Disease

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In the past decades, techniques of clinical neurophysiology have been helpful for characterizing various movement disorders, understanding their pathophysiology, and consequently guiding etiological research and therapy. However, people pay less attention in this special filed and not many neurologists are familiar with it. For assessing characters of Parkinson's disease (PD) and other movement disorders, surface electromyography with other techniques (e.g. EEG) are commonly used to clarify and identify the unique parkinsonian tremor from other forms of tremor, and are useful for detecting movement disorders similar to tremor, e.g. myoclonus. [1-3] The recent development of non-invasive brain stimulation, e.g. transcranial magnetic stimulation (TMS), allow people to assess the motor cortical functions. Furthermore, repetitive TMS (rTMS) has shown the ability to induce plasticity changes in the brain, and been used for investigating the human plasticity functions and even for treating diseases. For instance, TMS studies on motor complications of PD show that levodopa induced dyskinesia is related to aberrant reversal of plasticity[4] and the abnormal interaction between the frontal and motor cortices[5]. Freezing of gait may related to the supplemental motor area and improved by rTMS over that area[6]. However, larger series of randomised controlled trials showed inconsistent results in improving PD symptoms using rTMS[7, 8].

Although rTMS and other non-invasive brain stimulation techniques have shown the usefulness and potentials in disease investigation and therapy, their modulation effects are restricted in the surface of the brain. Newer techniques to overcome this problem are in need for modulating the function of deeper structures of the brain, e.g. basal ganglia. Focus ultrasound (FUS) has recently drawn people's attention for its ability to focus its energy at a site distant from the probe. It is better known to use high energy to increase temperature for tissue ablation9. However, FUS at a lower intensity causing no thermal effect may have higher potentials for treating PD in the future. Low intensity FUS (LIFUS) with microbubbles have shown the ability to open the blood brain barrier (BBB) to improve drug delivery to the brain10, 11. Recent studies found that similar but further advanced techniques can be used to open BBB and deliver genes without viral vectors to the basal ganglia to improve PD mice12, 13. On the other hand, it has also been noticed that LIFUS is capable of modulating the neuronal activity during, even after, the stimulation period in animals and humans14-19, and tremor in a rat model was improved by LIFU20. Such ability of neuromodulation of LIFU, which may be caused by altering the ionic conductance of neurons and astrocytes 21, opens another window for treating patients with PD and other neurological/psychiatric disorders in the near future.

**HIFU**: high intensity focused ultrasound
High acaoustic energey
Thermal effect
*Invasive*
**Application**(s): Tissue ablation

HIFU
LIFU

**LIFU**: low intensity focused ultrasound
Low acaoustic energey
No thermal effect
*Non-invasive*
**Application**(s): BBB opening for drug/gene delivery
Neuromodulation

*Figure Legend: Although FUS is better known to use high energy (HIFU) for tissue ablation, the non-thermal low intensity version (LIFU) has shown the ability to open BBB for drug or gene delivery in the brain and has the potential for neuromodulation, virtually, at any part of the brain.*

Clinical Neurophysiology and Non-Invasive Brain Stimulation for Parkinson's Disease, *continued on p. 28*

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**References**


1. Apartis E. Clinical neurophysiology in movement disorders. Handbook of clinical neurology / edited by PJ Vinken and GW Bruyn 2013;111:87-92.
2. Merchant SHI, Vial-Undurraga F, Leodori G, van Gerpen JA, Hallett M. Myoclonus: An Electrophysiological Diagnosis. Mov Disord Clin Pract 2020;7(5):489-499.
3. Vial F, Kassavetis P, Merchant S, Haubenberger D, Hallett M. How to do an electrophysiological study of tremor. Clin Neurophysiol Pract 2019;4:134-142.
4. Huang YZ, Rothwell JC, Lu CS, Chuang WL, Chen RS. Abnormal bidirectional plasticity-like effects in Parkinson's disease. Brain 2011;134(Pt 8):2312-2320.
5. Ponzo V, Picazio S, Benussi A, et al. Altered inhibitory interaction among inferior frontal and motor cortex in l-dopa-induced dyskinesias. Mov Disord 2016;31(5):755-759.
6. Mi TM, Garg S, Ba F, et al. High-frequency rTMS over the supplementary motor area improves freezing of gait in Parkinson's disease: a randomized controlled trial. Parkinsonism Relat Disord 2019;68:85-90.
7. Hamada M, Ugawa Y, Tsuji S, Effectiveness of rTms on Parkinson's Disease Study Group J. High-frequency rTMS over the supplementary motor area for treatment of Parkinson's disease. Mov Disord 2008;23(11):1524-1531.
8. Shirota Y, Ohtsu H, Hamada M, Enomoto H, Ugawa Y, Research Committee on r TMSToPsD. Supplementary motor area stimulation for Parkinson disease: a randomized controlled study. Neurology 2013;80(15):1400-1405.
9. Elias WJ, Lipsman N, Ondo WG, et al. A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor. N Engl J Med 2016;375(8):730-739.
10. Hynynen K, McDannold N, Sheikov NA, Jolesz FA, Vykhodtseva N. Local and reversible blood-brain barrier disruption by noninvasive focused ultrasound at frequencies suitable for trans-skull sonications. Neuroimage 2005;24(1):12-20.
11. Hynynen K, McDannold N, Vykhodtseva N, Jolesz FA. Non-invasive opening of BBB by focused ultrasound. Acta Neurochir Suppl 2003;86:555-558.
12. Lin CY, Hsieh HY, Chen CM, et al. Non-invasive, neuron-specific gene therapy by focused ultrasound-induced blood-brain barrier opening in Parkinson's disease mouse model. J Control Release 2016;235:72-81.
13. Wu CY, Huang RY, Liao EC, et al. A preliminary study of Parkinson's gene therapy via sono-magnetic sensing gene vector for conquering extra/intracellular barriers in mice. Brain Stimul 2020;13(3):786-799.
14. Fini M, Tyler WJ. Transcranial focused ultrasound: a new tool for non-invasive neuromodulation. Int Rev Psychiatry 2017;29(2):168-177.
15. Lee W, Kim H, Jung Y, Song IU, Chung YA, Yoo SS. Image-guided transcranial focused ultrasound stimulates human primary somatosensory cortex. Sci Rep 2015;5:8743.
16. Legon W, Ai L, Bansal P, Mueller JK. Neuromodulation with single-element transcranial focused ultrasound in human thalamus. Hum Brain Mapp 2018;39(5):1995-2006.
17. Legon W, Bansal P, Tyshynsky R, Ai L, Mueller JK. Transcranial focused ultrasound neuromodulation of the human primary motor cortex. Sci Rep 2018;8(1):10007.
18. Mueller J, Legon W, Opitz A, Sato TF, Tyler WJ. Transcranial focused ultrasound modulates intrinsic and evoked EEG dynamics. Brain Stimul 2014;7(6):900-908.
19. Daniels D, Sharabi S, Last D, et al. Focused Ultrasound-Induced Suppression of Auditory Evoked Potentials in Vivo. Ultrasound Med Biol 2018;44(5):1022-1030.
20. Sharabi S, Daniels D, Last D, et al. Non-thermal focused ultrasound induced reversible reduction of essential tremor in a rat model. Brain Stimul 2019;12(1):1-8.
21. Tyler WJ, Tufail Y, Finsterwald M, Tauchmann ML, Olson EJ, Majestic C. Remote excitation of neuronal circuits using low-intensity, low-frequency ultrasound. PLoS One 2008;3(10):e3511.

# *Deep Brain Stimulation: A Case-Based Approach* – An Interview with the Authors

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— *Pravin Khemani, MD, Movement Disorders Specialist, Swedish Neuroscience Institute, Seattle, WA, USA*
— *Michael Okun, Michael Okun, MD, Adelaide Lackner Professor and Chair of Neurology, Executive Director, Norman Fixel Institute for Neurological Diseases, University of Florida Health, Gainesville, FL, USA*


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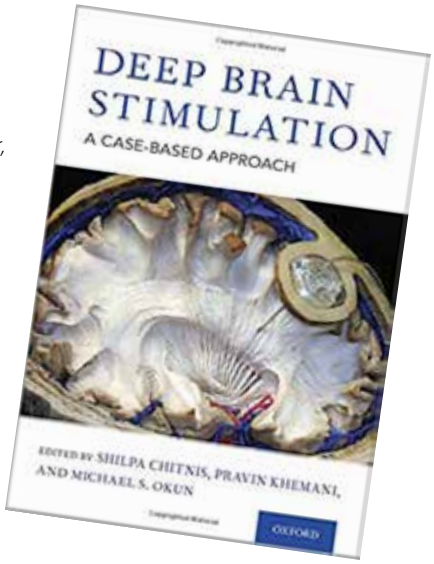
*Michael Okun*




Daniel Martinez, a member of the ***Moving Along*** Editorial Board, reached out to the authors of ***Deep Brain Stimulation: A Case-Based Approach*** to learn more about their new book.

**What is the highlight of this book? How does it differ from other DBS books?**

**Michael Okun:** This book reviews all of the core principles required to successfully manage DBS devices and it accomplishes this goal in the context of real-life successes and failures. We provide a meaningful discussion for each case, which is followed by a list of clinical pearls aimed at enhancing decision making within a clinical setting.

**Shilpa Chitnis:** Many DBS books in the past have focused almost exclusively on the theory of DBS programming; what adjusting amplitude and voltage does, what adjusting pulse width will accomplish... For a new learner and even for relatively seasoned learners, a patient (i.e. person) related perspective is important. We decided that it would make the most sense to present DBS patient management and programming through real life patient cases. The highlight of the book is that it walks the reader through the disease course of the patient; what they presented with, why they qualified for DBS surgery, what complications emerged and what approach was taken to address the issues. Our book helps the learner to effectively manage a complex thought process, which may include medication management, surgical issues and DBS programming. We believe that it is best to learn from real life examples.

**Michael Okun:** The contributors to the book are among the current and rising stars in the DBS field-- and they have shared the bread and butter cases as well as the more complex issues, which may emerge when managing this population.

**Who is the book directed to?**

**Pravin Khemani:** The book is directed towards healthcare teams caring for DBS populations (nurses, advanced practice providers, neurosurgeons and neurologists). This book will also be useful for neurology and neurosurgery residents and fellows in training.

**What do you expect the readers take away from this book? What is the key message in this DBS book?**

- There can be a systematic approach to DBS that will maximize success in both simple and complex clinical scenarios.
- The book provides expert advice with easy to read and digest clinical pearls.
- The book addresses guidelines and programming techniques for straight-forward as well as challenging DBS case management.
- This book will strengthen fundamental DBS techniques as well as expand the skills necessary for troubleshooting more difficult patient presentations.

**What were the key challenges you faced when editing this book?**

We worked hard to condense the cases into a digestible format with clinical pearls. The challenge of a great book is making it a great read.

**What do you recommend, do you have any advice, to anyone who is interested in starting in the process of editing a book?**

- The key is finding a topic you are passionate about.
- The vision for the book must be clear.
- Recruit experienced authors and co-editors.
- Make sure you have the bandwidth to run a project like this as it could take hundreds of hours.
- A great book writing experience requires patience, resilience, perseverance and dedication.

# MDS-AOS Digital Technology Primer for Neurologists: The Changing World of Practices in Parkinson's Disease

— *Prashanth L. Kukkle (LK), DM, Neurologist & Movement Disorder Specialist, Vikram Hospital, Bangalore, India*

*Prashanth LK*

Digital revolution has been the buzz since the beginning of this century. Digital technology has dramatically changed every aspect of our life in last two decades. Health care has not been far behind and currently the various digital technologies including artificial intelligence, virtual reality/augmented reality, 3D printing, robotics and nanotechnology has been slowly entering the realm of clinical care. The International Parkinson and Movement Disorder Society (MDS) has been upfront in amalgamating the technology to the clinical side. The Task Force on Technology, chaired by Dr. Alberto Espay and Prof. Walter Maetzler, have been at the forefront of these activities. This MDS-AOS Digital Technology Primer was a continuation of understanding and implementation of technologies in daily practice. This course was directed by Prof. Roongroj Bhidayasiri and was a perfect integration of technology during this COVID-19 pandemic. All of the lectures and slides were made available online on October 10, 2020 for all registrants to listen to the didactic talks at their own pace. On October 17, a Live Q&A session was held with all the speakers and course participants to give this technology primer an interactive phase. The topic were vast and varied and included on adopting technology in daily practice, methods of data acquisition, understanding artificial intelligence and deep learning, technology based phenotyping, patient centred outcome measures and telemedicine. The session was attended by registrants across the globe. Below are excerpts of the technology primer interview with the speakers.


**Prashanth LK: Prof. Roongroj, What made you think of arranging a Technology Primer session?**

**Roongroj Bhidayasiri:** The main reason that I was organizing this course was related to my own experience initially when conducting research with computer engineers that they didn't understand clinical aspects of PD. Likewise, when they discussed about the analytics with our clinical data and objective data, we as neurologists didn't understand either. Experience is also similar in several neurology congresses that I have attended. At my center, we started a lecture series on data science for neurologists, which was well received and became popular. As a result, I was taking it further to develop the course for the AOS. As this course became virtual, it opened the opportunity for global audience and we are grateful for the high interest of MDS members, not limited to the MDS-AOS, also with new members from engineering field. According to our Secretariat, we have so far 1,667 registrations from 73 countries/territories.

**Prashanth LK: Do you think Movement Disorders subspecialty is at the doorsteps of a major technological boost? (If yes, can you provide a couple of examples?)**

**Roongroj Bhidayasiri:** In my own view, I do not think that we can avoid technologies as they are already at our doors. However, we should learn how to use technologies wisely. I am trained as a clinician so I still have a strong belief in clinical acumen for managing patients. However, we should empower ourselves to technologies and learn what they can do for us. Technologies do the work for us (like monitoring) but we decide what is best for our patients.

**Prashanth LK: Prof. Espay, How do you think MDS can work to collate global work on AI and digital interfaces in the management of Parkinson's disease?**

**Alberto Espay:** Global work on AI as applied to Parkinson's disease remains focused on adding granularity to the world as we know it, rather than reinventing it altogether. The resulting digital interfaces seem electronic, automated versions of the analog world. MDS is in a unique position to encourage the analytic versatility of AI and, in particular, machine learning and deep learning to shine light into our blind spots and offer us a new vision of the many types and expressions of disease across the individuals affected. Machine learning offers much promise for applications aimed at individualizing the assessment of fluctuations and predicting such complications as freezing episodes and falls.

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**Prashanth LK: Most of the technological data help in assessment of motor symptoms. How to address the collection of digital non-motor symptoms in movement disorders?**

**Alberto Espay:** Except for aspects of autonomic dysfunction, most other non-motor symptoms, such as cognitive impairment, depression, anxiety, and pain are internal experiences that are elusive to current mHealth applications and require active input by patients. A future "e-Diary," designed by the combined work of the MDS Task Force on Technology and the MDS Ratings Scales Program Committee, promises to launch a platform for uncovering the burden and fluctuations associated with both the motor and non-motor symptoms of an individual. This would require integrating the input from patients regarding their view about perception and capacity at various times and the input from passive sensor data, strategically collected in the background. Over time, machine learning would preclude the need for active input to generate an accurate and personalized landscape of fluctuations. Working in the spirit of a true diary, this will be a large step forward from the patient diaries of the digital world.

**Prashanth LK: Prof. Maetzler, which patient centric digital resources are currently at the doorsteps of mass utilization and their strengths?**

**Walter Maetzler:** I start here with the strengths that digital biomarkers have for evaluating performance in the domestic environment. First and foremost, they open the door to an area and a phase in the life of a patient that has not yet been accessible to the medical professional yet. This is not only a relevant gain in clinically relevant knowledge, but actually an access to the most relevant time and place for the patient's quality of life and well-being. Another strength is the potentially possible option of measuring these biomarkers with a high degree of accuracy and repeatability. No instrument developed in the world to date can do this. Of course, these digital biomarkers also have enormous weaknesses, or, perhaps better said, birth pangs. Indeed, I am convinced that many, if not all, of these weaknesses can be eliminated by consistent testing and validation.

What are the most promising parameters that may soon find their way into clinical routine? In my opinion, we can assume that digital parameters that evaluate physical activity and mobility as well as sleep behavior will first be integrated into clinical routine. These parameters may be relevant for many diseases, since they change in connection with many diseases. For Parkinson's disease, we will probably have access to easy-to-use devices and validated algorithms for the assessment of the occurrence and severity of, e.g., hypokinesia, tremor, gait disturbances and motor fluctuations.

**Prashanth LK: Do you think collecting daily based digital data would be a boon or nuisance in daily clinical practice?**

**Walter Maetzler:** I believe that this data will be a blessing. But we still have to solve some problems until then. First of all, the data must be prepared in such a way that a human brain suffering from a disease (i.e., the brain of a patient) or managing diseases (i.e., the brain of the medical professional treating the patient), which does not do complicated computer exercises every day, can interpret it quickly and correctly. By the way, I am in favor of the medical professional and the patient having access to exactly the same data, so that there are no different interfaces and data accesses or analyses. Only in this way can we ensure that the addition of digital data to clinical and patient practice works so well that all stakeholders involved can reap the benefits: To quickly gain, in the patient - medical professional conversation, an overview of the restrictions of everyday life caused by the disease and which limit the quality of life of the affected person, and then to have as much time as possible to jointly develop a good plan for the next months in order to leave the disease as little space as possible in everyday life.

**Prashanth LK: Prof. Chou Ching Lin, given most of the physiological data acquisition in clinical practice happens in well controlled environments, how do you think, these factors affect in daily recordings and how to overcome these in mass digital data collection?**

**Chou Ching Lin:** This question is very general and strongly dependent on the development of technology. First of all, it depends on what is the goal. For example, if the goal is to detect the occurrence of certain rare events, then, it might be less important to have good signal quality from start to the end. However, if the goal is to monitor the trend and require, it usually will fail. For example, the calculation of heart rate variability is very sensitive to motion artifacts. The sensor needs to be fixed properly, otherwise the calculation is impossible. The other way to alleviate the problem is to develop a better and specific method for signal processing. For most electrophysiological signals, I think motion is still an obstacle needing more researches. Other problems, such as memory capacity, wireless transmission or power capacity, are less critical today.

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**Prashanth LK: Dr. Peerapon, Internet of things (IOT) does look like future of data interpretation. What type of co-ordination / platform upgradation is required from the Movement Disorders specialist community to be IOT ready?**

**Peerapon Vateekul:** Yes, I agree that IoT will play an important role in the data collection for movement disorder. There are many platforms that IoT can be applied, e.g., gait data (waling pattern), hand (tremor), etc. Also, nowadays there is an advancement of video analytics, so we can analyzed movements from videos instead of using sensors.

**Prashanth LK: With the HIPAA (Health insurance portability and accountability act) privacy issues and ethical considerations limitations in medical practice, how we can overcome (or what modifications are required) to implement IOT across the geographical boundaries?**

**Peerapon Vateekul:** This is one the most mentioning topics in AI. There is a new concept called "collaborative learning" that many organizations can exchange the AI models without sharing patient's sensitive data. Please find the links below about this concept from NVIDIA, where Chulalongkorn University is also part of this network.

https://developer.nvidia.com/blog/federated-learning-clara/

https://www.cutechcenter.com/federated-learning.html

**Prashanth LK: COVID-19 lockdown restrictions have completely changed the concepts of Telemedicine. Currently telemedicine has become one of the main stays of care in PD. What modifications in approach is required by physicians to address clinical assessments and prescription related issues?**

**Onanong Phokaewvarangkul:** Thank you very much for this question. The COVID-19 situation has influenced significant changes in medical practices for PD. Because of social isolation and other drastic (but necessary) measures, concerns involving care in PD cases are emerging. Therefore, the role of telemedicine has shown the potential to enable maintenance care in PD cases without any risk of exposure to infection at healthcare facilities. However, changing day-to-day medical practices from conventional in-person visits to telemedicine may raise concerns among some physicians due to the difficulty inherent with conducting physical examinations and the complexity of telemedicine-device utilization. In addition, conventional in-person visits offer better, more thorough, and accurate diagnosis and treatment plans compared to telemedicine.

Therefore, adjustments to certain aspects of medical practices may be helpful to maintain effective control via telemedicine, such as: 1. Modification in the diagnosis or clinical assessment approach; 2. Modification in the management approach

**1. Modification in the diagnosis or clinical assessment approach**

Because of the visual nature of PD examination and the ability to capture it on video, telemedicine is suitable for the evaluation of PD patients concerning assessment for facial expression, bradykinesia of the upper and lower extremities, tremors, and walking patterns; motor fluctuations and dyskinesia can be detected from videos. Therefore, detecting these signs via telemedicine can help physicians to confirm the diagnosis and make adjustment for the most suitable treatment for PD cases. In addition, telemedicine can help physicians to remotely monitor PD patients who receive advanced therapy, thus enabling early detection if their patients encounter problems.

**2. Modification in the management approach**

Because COVID-19 infections may account for either direct or indirect effects, the different approaches used to treat patients need to be personalized. For subjects infected with COVID-19, the direct effect of this infection usually targets motor deterioration. In such a case, continued usage and increased dosage of anti-Parkinsonian medication is recommended. For PD patients who are not with COVID-19, the indirect effects of this infection are usually related to psychological stress and physical inactivity due to fear, social isolation, and lack of healthcare resources, which can then worsen Parkinsonian symptoms in terms of motor and non-motor issues. In this case, a combination of treatment including clinical and psychological support is suggested.

**Prashanth LK: Dr. Do-Young Kwon, What are the current major hurdles in implementing the technology in daily practice?**

**Do-Young Kwon:** Many studies showed that satisfaction was higher in new technology user group. Meanwhile, frequent reason for withdrawal was technical difficulties by senior patients.

Truly, there are still many barriers to widespread use of technologies to daily practice, such as limitation of accessibility, usability issue due to intrinsic age barriers and dexterity problem in PD patients.

Caregivers need to provide help with the set-up and support to secure the condition prior to use.

And the makers of the device need to develop user-friendly alternatives that can support them: such as adopting voice recognition technology rather than keyboard-based approach

Reimbursement and licensing, regulation problems and technological limitations are another problem.

I think this is a matter of time. As already mentioned, COVID-19 hasten these changes.