Endorsement letters:

Dr Angela Deutschlander – purchased NMP for clinical research:

conducting pilots towards day-to-day implementation

Prof Michele Hu – purchased NMP for clinical research:

Early assessment in prodromal cohors and symptom monitoring for the MJ Fox Parkinson's Progression Marker Initiative

Prof David Owens – purchased NMP for a future application:

optimising anti-psychotic drug dosage to avoid motor side effects

Dr Carol Routledge Alzheimer's UK / Small Pharma London:

Future application in early detection of Alzheimer's disease

Milos Ivanovic – purchased NMP for a future application:

Early assessment of traumatic brain injury

Please also see the spoken endorsement from Prof Richard Walker at the Northumbria NHS Foundation Trust,

who has implemented the NeuroMotor Pen in the NHCFT Trust

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Ihre Zeichen, Ihre Nachricht vom:	Unsere Zeichen:	Durchwahl:	Datum:
	De-se	15008	21.10.2020

Re: NeuroMotor Pen application in Germany and in the US

To whom it may concern

I am a Consultant Neurologist and Neuroscientist from the Department of Neurologyat the University Hospital in Magdeburg, Germany. I previously held a senior role in the Mayo Clinic, where I focused on Movement Disorders and Neurogenetics.

I strive to combine my clinical work with research activities always. One of my research interest is in the differential diagnosis of atypical Parkinsonian syndromes and M. Parkinson. I authored several papers on this topic, e.g., 'Atypical Parkinsonian syndromes, a general neurologist's perspective', which explains some of the challenges and the use of neuroimaging techniques.

Building the second largest DNA bank of patients with Parkinson's disease in Germany and leading several outpatients´ clinics for Movement Disorders I have over 20 years of experience with the challenges of establishing a diagnosis in the early disease stages. Diagnosing Movement Disorders and delivering the best possible treatment for these patients is an area close to my heart and an important research area for me.

During the Movement Disorder Society (MDS) 2019 conference, I had the great pleasure to hear about the NeuroMotor Pen product and its fantastic potential to support diagnostic decision making through quantitative assessment of hand and arm movements. Based on the clinical validation studies so far, I think there is a huge potential for the NeuroMotor Pen to find its way into every day clinical practice for use within the specialist's office and reduce the need for brain imaging, such as DaTSCAN. The latter is always burdensome. Moreover, DaTSCAN confirms a dopamine deficiency only and only rarely allows differentiating between the various atypical Parkinsonian syndromes, which are clinically heterogenous and show phenotypic overlap. The NeuroMotor pen appears to have similar capabilities with significantly reduced cost and patient burden. The pen's working principle are very intuitive as it quantifies the typical symptoms we look for when establishing a diagnosis.

In addition, for the purpose of patient monitoring when undergoing treatment or prior to starting treatment, the NeuroMotor Pen would complement the assessment of motor function with the MDS Unified Parkinson's Disease Rating Scale (MDS-UPDRS) with the benefit of objectivity and increased accuracy. The

Pen readings overlap with the symptoms we would normally rate using the MDS-UPDRS scores. In Germany, we are accustomed to evaluating patient's general well-being post-diagnosis every one, three, or six months, depending on the complexity encountered, which includes scoring motoric abilities (MDS-UPDRS). It is my firm opinion that the pen would significantly simplify our record keeping.

Another important application area is optimizing treatment for patient undergoing specialized treatments, such as deep brain stimulation or treatment with apomorphine, where accurate treatment assessment is also essential. I am currently in charge of setting up a new research group and outpatient clinic, and I am very interested in implementing the NeuroMotor pen in our research. I am also interested in providing guidance with regard to the product development and implementation in the care pathway both in Germany and in the USA.

I am excited about the potential of the groundbreaking innovation of Manus Neurodynamica and I look very much forward to working with the company.

Yours sincerely,

PD Dr. med. Angela B. Deutschlaender
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University of Magdeburg

UNIVERSITY OF OXFORD

DEPARTMENT OF CLINICAL NEUROLOGY

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12th May, 2020

Re: Manus Dynamica and NeuroMotorPen support letter

With this letter I would like to express my support to Manus Neurodynamica and their efforts to clinically implement the NeuroMotorPen. I envisage future applications of the digital motor measures using the NeuroMotor Pen for both earlier diagnosis and monitoring the progression of Parkinson's. Making an accurate diagnosis of Parkinson's disease currently requires a trained clinician applying clinical criteria. It is not unusual for delays to occur before a correct decision is reached. A certain number of Parkinson's patients may struggle for years trying to get a correct diagnosis, particularly where access to specialist movement disorders clinical input is limited. Therefore, the need for developing of non-invasive, accurate and objective test is of the vital importance to help the diagnosis. By providing quantitative, objective data to assist clinicians, I think that the NeuroMotorPen might play a key role addressing this issue, and has the potential to address a critical unmet need in the fight against Parkinson's disease.

The NeuroMotor Pen could potentially help doctors to diagnose Parkinson's accurately, early and in a clinically practical manner. I am interested in research to validate and test it in large numbers of subjects recruited from well-phenotyped PD cohorts using parallel clinical testing to ensure it is tractable and fit for purpose. The NeuroMotor Pen might provide an objective accurate motor skill market that has the potential for use in treatment optimisation along to the Unified Parkinson's Disease Rating Scale.

A final point is that the NeuroMotor Pen system is portable, can be operated without specialist expertise and allows digital record keeping. This makes the system suitable for remote monitoring of patients away from the clinic and at home or for the test to be administered in the waiting room. Therefore, the NeuroMotorPen could easily find a place in common medical practice in these three areas – differential diagnosis, pre-symptomatic diagnosis and monitoring of Parkinson's disease, both in the clinical and remote patient assessment.

Yours sincerely,

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21ST February, 2020

TO WHOM IT MAY CONCERN

I have been involved in research into the biology and treatment of major psychiatric disorders for nearly 40 years, including the psychopharmacology of antipsychotic drugs. A key part of my interest is the association of these essential treatment elements with undesirable effects that can be profoundly counter-therapeutic, especially movement disorders, and I have authored the only internationally available textbook on antipsychotic-related movement disorders [1].

All available drugs of the antipsychotic class act by attenuating the actions of the key brain messenger chemical, dopamine. While this is the essential therapeutic action in psychoses, dopamine is also instrumental in modulating motor function and antipsychotics have a marked tendency to promote drug-induced parkinsonism (DIP). According to the literature, this affects between 30 and 40% of patients. However, these figures depend on unreliable clinical examinations recorded on standardised rating scales, in which 'caseness' is predefined. The long-standing question of whether drugs which block central dopamine transmission *inevitably* produce DIP has never been

[1] Owens DG Cunningham. *A Guide to the Extrapyramidal Side-Effects of Antipsychotic Drugs* (2nd edition). Cambridge University Press, Cambridge. 2014.

PROFESSOR DG CUNNINGHAM OWENS, MD(Hons), FRCP, FRCPsych
Professor of Clinical Psychiatry

comprehensively addressed. DIP therefore represents both a major clinical, but also conceptual, challenge for psychiatry.

The 'gold standard' evaluation method of motor function is instrumentation but attempts to apply these principles using patient-centred 'pen-and-paper' methods lacked reliability and while movement disorder laboratories can enhance reliability, there are few in existence, they are resource-intensive and are intimidating for patients.

We have been fortunate in gaining access to the NeuroMotor Pen which, in my view, represents a sea-change in clinical assessment. In our pilot application, we have found the system to be entirely portable, easy to use and, most importantly, engaging and acceptable to patients, including those who are actively psychotic. It also appears that, from initial analyses, it provides more sensitive and reliable information than a standard clinical examination. I would predict that there is the potential for widespread application of this system in both research contexts and also in routine clinical therapeutics.

The research applications are, I believe, considerable, including exploring a number of theories at the heart of our understanding of antipsychotic pharmacology that remain unaddressed with evidence, including the theory of 'inevitability' in relation to DIP and 'anti-psychosis', the 'neuroleptic threshold' hypothesis proposing a graded relationship between EPS expression and efficacy, amongst others. Data acquired in these contexts might be extended to explore objectively the relationship between dopamine receptor occupancy and both efficacy and tolerability and the relationship between these and patient variables such as drug levels and metabolic status (CYP450 enzyme genotype) etc.

Furthermore, with increasing shift of emphasis in the major theory of aetiology of psychosis (the Dopamine Hypothesis) from a site of dysfunction beyond cell junctions (i.e. post-synaptically) to disorder sited before cell junctions (presynaptically), it is likely that new antipsychotics will be developed with a different (presynaptic) mode of action than hitherto used compounds. This system would be ideally suited to detecting parkinsonian risk with such novel compounds in comparison to standard drugs and comparing patterns of evolution.

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I also foresee great potential in routine clinical practice. While psychiatrists are good at monitoring mental state, they are poor at identifying DIP or else, if recognised, misattribute features to psychological rather than neurological causation. Despite exhortation for over 30 years by experts, including myself, that neurological effects should be routinely monitored, it remains the case that this is poorly and inconsistently undertaken by divers means that lack consensus, with findings variably recorded, if at all. An easy-to-use system, such as the NeuroMotor Pen, could be utilised by clinicians to improve routine psychiatric practice by providing a means of objective monitoring for DIP emergence/evolution from time of starting antipsychotics, while also aiding them in therapeutic choices relating to drug potency, dosage, rates of escalation etc.

With psychiatric practice dominated by compounds of similar modes of action, it can often seem to clinicians that there is little way forward for them to improve the quality of their practice, leaving prescribing choices devoid of skill and lacking subtlety, with little attempt at tailoring choices to individual need. I firmly believe, however, that improving how currently available drugs are used – that is, improving psychiatric *therapeutics* – offers a clear way of countering such negativism, enhancing psychiatrists' skills base while improving quality of care for individual patients.

The NeuroMotor Pen system, in my view, is the first system to offer a pragmatic and valid monitoring tool in psychiatry for many years, and the first ever to offer the realistic prospect of addressing one of our major conceptual and clinical problems. I am excited about its possibilities.

DG Cunningham Owens
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29 September 2020

To whom it may concern

I am Chief Medical and Scientific Officer of a small biotech company developing treatments for mental health disorders, but over the past 3.5 years I was Director of Research at Alzheimer's Research UK and managing Director of EDoN, a global, digital initiative focussed on the **e**arly **d**etection **o**f **n**eurodegenerative diseases. Prior to that I held a number of different roles within the Pharmaceutical and biopharmaceutical industry, both in the UK and US, where I was accountable for the implementation of neuroscience translational medicine strategies. With this letter I would like to express my support to Manus Neurodynamica and their efforts to implement the NeuroMotorPen™ in within both clinical practice and the pharmaceutical industry.

It is increasingly recognised that rigidity, slowness, gait impairment, and other disorders of movement accompany Alzheimer's disease at various stages of the illness. The presence of these so-called extrapyramidal features has been reported to predict disease prognosis and pathologic localization. Furthermore, such features are classically symptoms of dementia with Lewy bodies, but are also found to occur in vascular and frontotemporal dementia. In addition, they can be induced by cholinesterase inhibitors and other prescribed psychopharmaceuticals. Evaluating fine motor skills in movement disorder is a complex task – even for specialists – and an easily performed objective test of fine motor skill could aid in the diagnosis and management of those with suspected and established Alzheimer's and other dementias. Utilising the appropriate diagnostic tool may support the differential diagnosis of such disorders.

The NeuroMotor Pen™(NMP) is a convenient solution for the quantification fine motor skill that is capable of providing objective information about decline in cognition and motor skill with higher accuracy than clinical ratings scales. Moreover, electronic record keeping and remote assessment becomes possible.

As of yet, no other highly acute tests for fine movements have been successfully developed and validated yet and the NeuroMotor pen is one of the most promising solutions available, for which a very high specificity has already been demonstrated in other application areas, such as the differential diagnosis of Parkinson's disease. Combined with other tests, I envisage that the motor measures detected with the digital NeuroMotor Pen will be able to support identification of neurodegenerative diseases that cause decline of motor function, including Alzheimer's and other dementias.

To further validate the utility of the NeuroMotor Pen to support the differential diagnosis of neurodegenerative diseases it would be useful to collect additional data from subjects with these various disorders who, for example, are already taking part in longitudinal observational studies already set up in the UK and elsewhere. This would provide information on the use of the NeuroMotor digital pen as an individual tool diagnostic tool or as part of a more comprehensive combination of diagnostic tools.

Kind Regards,

Carol Routledge

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Endorsement letter

My name is Milos Ivanovic. I am a Neuro Critical Care physician and a Captain in the United States Army and prospective Executive MBA candidate at Booth School of Business..

In 2020 nearly 1 million people were living with Parkinson's disease in the US alone, and the number of affected people is expected to rise to 1 238 000 by 2031. Each year approximately 60,000 Americans are newly diagnosed. Often the first assessments for Parkinson's disease is made by family physicians, who normally seek an additional opinion from a neurologist with experience and specific training in the assessment of Parkinson disease. However, there are many neurological conditions that mimick Parkinson's disease including: essential tremor, normal pressure hydrocephalus, dementia with Lewy bodies, multiple system atrophy, Corticobasal syndrome, progressive supranuclear palsy. All these conditions are making accurate diagnosis of Parkinson disease a complex task even for experienced physicians. So far there are no specific, objective tests for Parkinson disease in outpatient setting. Diagnosis is based on medical history, review of signs and symptoms, neurological and physical examination. However, even specialists sometimes struggle to make a diagnosis as a large number of patients has overlapping, unclear symptoms, making DaTscan often necessary to reach the final diagnosis.

DaTscan protocol is complicated and the procedure that can take up to several hours and still need a specialist reading by neurologist or radiologist. Due to radiation, safety measures must be put in place in order to prevent exposure to clinical personnel and patient. Also, in order to minimize radiation dose to the bladder patients are encouraged to hydrate prior and following DaTscan administration, limiting its use in patients with congestive heart failure and chronic kidney disease -conditions often met in aging population. Also, before administration of DaTscan, Lugol solution or potassium perchlorate must be administrated in order to block uptake of radioactive iodine 123 by the patient thyroid gland.

The ioflupane within DaTscan binds to dopamine transporter. Thus, all drugs that bind to these receptors with high affinity may interfere with image acquisition. Lastly, DaTscan can potentially interfere with numerous drugs: Amoxapine, amphetamine, benztropine, bupropion, buspirone, cocaine, must not all, meds amphetamine, methylphenidate, nor ephedrine, phentermine, phenylpropanolamine, selegiline, sertraline. Selective serotonin inhibitors [paroxetine and citalopram] may increase or decrease binding to the dopamine transporters as well.

On the other hand, Manus NeuroMotor Pen is a device that is portable and easy to use, does not require special expertise and potencially allows incorporations of objective data in patient's electronical health records. All these characteristics may help physicians to diagnose Parkinson's disease accurately, early and in outpatient setting. In addition, it is completely noninvasive, quick and user friendly and do not require any preparation. It can be applied without hesitations to different patient populations regardless

of their educational, intellectual and socio-economic level. Due to its high sensitivity, it can help primary care physicians to catch the disease in its early stages before clinical symptoms develop. Also, it may help specialists monitor success of the medical treatment.

Due to enormous cost of care for Parkinson's patients, private healthcare insurance companies as well as Medicare and Medicaid will have great interest in supporting this device because it will expedite patient care and save billions of dollars in diagnostics and treatment. Especially now, when COVID 19 pandemic changed the way how medicine is practiced, limiting contact between patient and physician. Mobile, easy to use device that can be easily incorporated in telemedicine visit is most definitely way to go. Soon, it may find its place in every primary care practice as a helpful, inexpensive diagnostic tool.

It is my belief however that the NeuroMotor Pen device itself and proprietary analytical software will allow much broader application. As a Neuro Critical Care physician, I am interested in acute and chronic traumatic brain and spinal cord injuries. Repeated mild traumatic brain injuries lead to chronic traumatic encephalopathy. This relatively new medical entity is a degenerative disease that develops after repeated mild traumatic brain injuries like sports related concussions (best described in NFL and soccer players as well as in boxers), work, motor vehicle accidents or combat related traumatic brain injuries. This disease can be one of the most underrated factor of early onset dementia and Parkinsonism leading to significantly diminished life quality and life expectancy as well as increased lost income and health care costs. Furthermore, numerous neuromuscular diseases and conditions could be evaluated, and their therapy guided by analyzing hand-eye-brain coordination that NeuroMotor Pen does exquisitely.

At the end, I would like to wholeheartedly recommend this device for future development and application in hospitals and outpatient settings. Personally, I will aim to complete a proof of concept in traumatic brain injury and try to connect with colleagues to facilitate further collaborations in trials in the USA that will broaden NeuroMotor Pen use and reinforce already strong evidence from trials conducted in Europe.

Sincerely,

Milos Ivanovic MD