nQ Medical™

Pioneering a New Era of Precision Neurology
AI-Powered Digital Biomarkers for Neurodegenerative Diseases

An Introduction to the nQ Digital Biomarker Discovery Platform

"Time is Brain." To improve brain health, we must first measure it easily, reliably, and ubiquitously. nQ Medical was founded on the idea that the way we type yields a rich data stream with unique advantages for passive collection which when treated respectfully ensuring privacy first, collected in the right patients, and analyzed in the right way - can yield quantitative measurements of motor and cognitive symptoms to directly improve the lives of patients by enabling the promise of precision medicine in drug development and clinical care.

Whether two-handed touch-typing or pecking with a single finger, typing is a complex activity requiring the engagement of multiple motor and cognitive processes[1] of the brain and neuromuscular systems. Even without knowing *what* we are typing, the exact dynamics of *how* we press keys when typing – the milliseconds from the top to bottom of a keystroke, the pauses, hesitations, bursts create a complex pattern which carries enough information about us to be unique to each individual – like a fingerprint. In fact, the study of keystroke dynamics has its origins in the field of biometric security[2] where authentication of the dynamics of *how* a user types can add a layer of protection beyond simply authenticating *what* is the correct password. Unlike a static fingerprint however, the patterns in keystroke dynamics can vary with changes in users' psychomotor state and reflect changes in the underlying neurologic systems which occur over minutes, weeks, or years.

To date, nQ Medical has conducted multiple clinical trials[3,4,5,6,7,8] at leading academic institutions in real patients to empirically answer the question: can meaningful clinical insights be successfully extracted from typing keystroke dynamics data (without capturing the content of what patients are typing)? For fatigue in healthy subjects, motor symptoms of Parkinson's Disease (PD), mild cognitive impairment (MCI), dementia, motor/functional symptoms of Amyotrophic Lateral Sclerosis (ALS i.e., Lou Gehrig's Disease) we have shown this is possible. Our biomarker pipeline is most advanced within the disease area where we have most experience: Parkinson's disease; where we have developed biomarkers to aid diagnosis, to track symptoms over time, and to identify dopamine responders vs non-responders[6] all progressing through varying advanced stages of clinical validation. Importantly, we have demonstrated ability to go beyond motor symptoms to measure cognitive symptoms in patients with MCI and

"Even without knowing what we are typing, the exact dynamics of how we press keys when typing is unique to each individual – like a fingerprint."

dementia and assess not only global cognition but specific cognitive subdomains[7]. Other symptom and disease specific digital biomarkers (e.g., fatigue, ALS) have also been demonstrated in principle. Clinical validation for these additional indications is ongoing following a path similar to our PD biomarkers and novel indications are regularly being added.

"nQ has demonstrated ability go beyond motor symptoms to measure cognitive symptoms and assess specific cognitive subdomains."

Experience across multiple disease areas has led to development of a streamlined process of pilot studies, algorithm development, followed by multi-phase clinical validation allowing for rapid testing and deployment of the technology into new diseases and phenotypic areas. Success in healthy patients and across multiple disease areas demonstrates the technology goes beyond disease-specific biomarkers and instead represents a generalizable platform for quantification of neurologic motor and cognitive symptoms across diseases with potential applications spanning research, development, and clinical care settings.

In biopharmaceutical drug development realm, the nQ platform can yield biomarkers to add value in nearly every phase of clinical development: from pharmacodynamic biomarkers for neurocognitive disorders to deep phenotyping in natural history studies of rare and common diseases to enrichment strategies and adaptive designs for clinical trials to post-approval surveillance and marketing insights.

Pharmacodynamic Biomarkers: Criteria for selection of successful drug targets and disease areas for drug development includes the availability of pharmacodynamic biomarkers to guide early go/no-go decisions and establish value creation. The ability to measure motor and cognitive symptoms reliably and passively through sensitive digital biomarkers opens up entire disease areas for investigation. For example: cognitive symptoms in neurodegenerative diseases (e.g., Alzheimer's Disease) often progress slowly over many years resulting in challenging clinical trial timelines usually intractable to all but the largest pharmaceutical companies with huge budgets, large numbers of patients, measuring expensive/invasive biomarkers over many years[9]. A digital biomarker developed using the nQ platform for sensitive detection of cognitive impairment and tracking small changes in cognitive function over time could address this by enabling the design of more efficient clinical trial strategies. A sensitive digital biomarker may detect early evidence of efficacy during Phase I and II trials to aid POC and establish value of the development program to inform partnership/fundraising decisions and to inform go/no-go investment decisions for expensive Phase III trials. In a Phase III trial yielding only modest/noisy effects on primary clinical outcome at an early timepoint, inclusion of a digital biomarker secondary outcome showing convincing effect can bolster argument to FDA[10] of the therapy's likely significant clinical benefit over longer time scales.

Enrichment Biomarkers: In an approach consistent with the FDA's guidance to industry for clinical trial enrichment strategies[11], digital biomarkers developed using the nQ platform could be deployed across populations of patients to pre-screen or segment patients in order to increase predictive enrichment, decrease variability, or increase prognostic enrichment to allow for more efficient, better powered clinical trials. For example: sensitive digital biomarkers can help identify early

responders and non-responders to a therapy during a run-in period, greatly enhancing the benefit-risk relationship for patients and increasing the trial's probability of success. For another example: patients all with very similar stage of PD could more accurately be segmented by complementing traditional approaches with digital biomarkers rather than relying solely on UPDRS measured at a single clinical visit (with significant intra-patient variability[12]) or solely relying on Hoehn and Yahr stage (with significant intra-stage heterogeneity[13]). A final example: inexpensive digital biomarkers could be used to pre-screen patients and increase the yield of subsequent very expensive/invasive testing such as PET scans or lumbar punctures to identify patients at highest risk for a clinical endpoint[14].

Natural History Studies: Drug development programs, often with indications in rare disease, may undertake critical natural history studies to aid development of biomarkers, selection of outcomes, establishment of historical controls, and to raise awareness of the disease[15]. Integration of the nQ platform at these earliest stages of a drug development program will allow deep phenotyping of patients and generation of real-world evidence with the greatest flexibility yielding better insights and more useful novel biomarkers for subsequent clinical trials.

Real World Data: Digital biomarkers of neurologic function represent real world evidence which can be combined with other clinical data to generate real world evidence. For example: deployment of digital biomarkers to users of a drug post-approval can be useful to help demonstrate efficacy in phase IV studies for therapies with accelerated/ restricted approvals. Additional example: this type of RWE can further help drugmakers understand product use, adherence, and performance in the real world among different subgroups and geographies and be useful to value justification, label expansion, and pricing strategies. A final example: inexpensive digital biomarkers can be helpful in the clinic to aid effective screening of patients with neurologic disease to identify candidates for new treatments as they become available.

SaMD in the Clinical Setting: nQ Medical has received FDA breakthrough device designation for Parkinson's Disease. A patient with PD faces an average delay of 10 years from first noticeable symptoms to diagnosis[16]. We aim to address this gap by aiding clinicians in PD diagnosis through digital biomarkers that quantify PD symptoms and help track symptoms over time. Similarly, for patients with cognitive decline, we believe nQ biomarkers can aid with easier, earlier diagnosis and more reliable tracking of symptoms allowing primary care and specialist clinicians to deliver better care.

Today's healthcare system reflects a world without effective disease-modifying therapies for neurodegenerative diseases where we continue to lack effective mechanisms for early diagnosis or effective screening of patients, often because providers feel there isn't much to be done about neurodegeneration. While some limited efforts such as new cognitive screening laws passed in Massachusetts[17] aim to combat this current nihilism, developers of early disease modifying therapies for neurodegenerative diseases continue to face an uphill battle to effectively screen and identify patients at early stages of disease to start

"nQ Medical has received FDA breakthrough device designation for Parkinson's Disease."

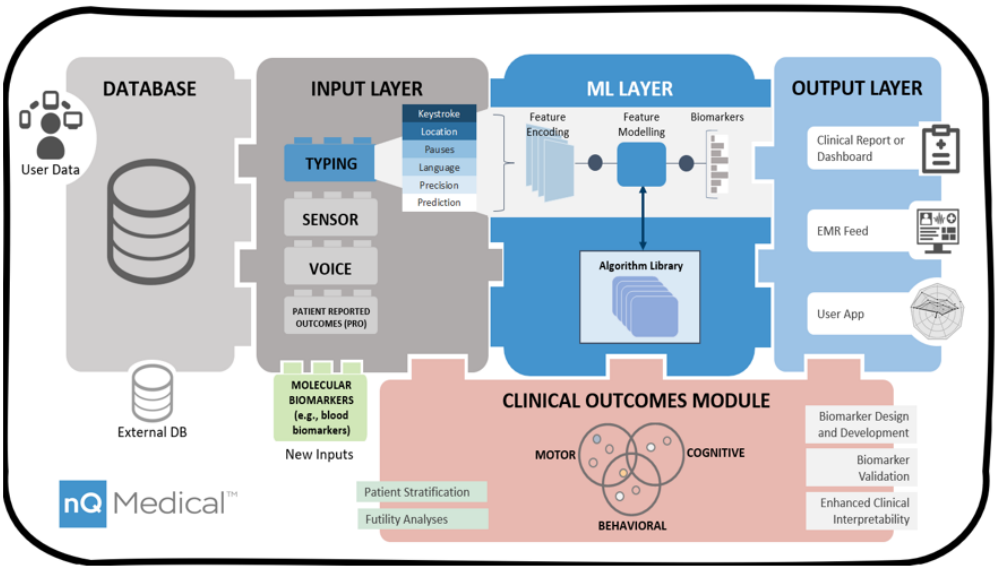
treatment. Even today, without disease-modifying therapies for neurodegenerative conditions, early and better diagnosis remains an important goal for many patients and families[18] in order to reduce uncertainty, live independently for longer time, improve quality of life, start drug and non-drug treatments, consider enrollment in clinical trials and inform fraud protection[19], financial and legal planning. While neurologic symptom screening can be accomplished today by repeatedly subjecting patients to a battery of tests, we believe our methods for passive, continuous background measurement of symptoms is critical to effective deployment at scale with high compliance and reliability.

Ongoing clinical trials designed in collaboration with FDA will support our PD medical device 513(f)(2) De Novo Classification request with plans for additional indications in PD and other disease areas to seek clearance via 510(k) premarket submissions. Through analysis of keystroke dynamics, nQ Medical has generated a platform which respects patient privacy while effectively quantifying motor and cognitive neurologic symptoms via passive data collection. The clinical insights gleaned from this platform will grow more powerful and ubiquitous as digital devices grow more pervasive and with growing comfort of the healthcare and pharmaceutical sectors with digital biomarkers.

"nQ's methods for passive, continuous background measurement of symptoms is critical to effective deployment at scale with high compliance and reliability."

The deep phenotyping enabled by these digital biomarkers will benefit patients by enabling effective development of new therapies and helping match the right patient to the right treatment.

nQ Digital Biomarker Discovery™ Platform



1. Meet Pharma's Desire for Digital Biomarkers to Expedite Drug Dev
2. Precision Neurology to Address Need for Early Detection, RPM, Treatment
3. Address Aging Population's Demand for Brain Health Assessment and QoL

Disclaimer and Forward-Looking Statements: This report contains forward-looking statements regarding nQ Medical products and development. Such forward-looking statements are based on the company's assumptions, estimates, outlook, and other judgments made in light of information available at the time of preparation of such statements and involve both known and unknown risks and uncertainties. Accordingly, plans, goals, and other statements may not be realized as described, and actual financial results, success/failure or progress of development, and other projections may differ materially from those presented herein. Information concerning biomarkers and diagnostics (including those under development) contained herein is not intended as advertising or as medical advice.

References:

1. Hayes, J. R. & Chenoweth, N. A. Is Working Memory Involved in the Transcribing and Editing of Texts? *Writ. Commun.* **23**, 135-149 (2006)

2. Monrose, F. & Rubin, A. D. Keystroke dynamics as a biometric for authentication. *Future Gener. Comput. Syst.* **16**, 351–359 (2000).

2. Giancardo, L. *et al.* Computer keyboard interaction as an indicator of early Parkinson's disease. *Sci. Rep.* **6**, 34468 (2016).

3. Arroyo-Gallego, T. *et al.* Detecting Motor Impairment in Early Parkinson's Disease via Natural Typing Interaction With Keyboards: Validation of the neuroQWERTY Approach in an Uncontrolled At-Home Setting. *J. Med. Internet Res.* **20**, e9462 (2018).

4. Arroyo-Gallego, T. *et al.* Detection of Motor Impairment in Parkinson's Disease Via Mobile Touchscreen Typing. *IEEE Trans. Biomed. Eng.* **64**, 1994–2002 (2017).

5. Giancardo, L., Sánchez-Ferro, A., Butterworth, I., Mendoza, C. S. & Hooker, J. M. Psychomotor Impairment Detection via Finger Interactions with a Computer Keyboard During Natural Typing. *Sci. Rep.* **5**, 9678 (2015).

6. Matarazzo, M. *et al.* Remote Monitoring of Treatment Response in Parkinson's Disease: The Habit of Typing on a Computer. *Mov. Disord.* **34**, 1488–1495 (2019).

7. Ashley A. Holmes, Shikha Tripathi, Emily Katz, Ijah Mondesire-Crump, Rahul Mahajan, Aaron Ritter, Teresa Arroyo-Gallego, and Luca Giancardo. A novel framework to estimate cognitive impairment via finger interaction with digital devices; [Submitted]. *Brain Commun.* (2021).

8. Cummings, J., Reiber, C. & Kumar, P. The price of progress: Funding and financing Alzheimer's disease drug development. *Alzheimers Dement. N. Y. N* **4**, 330–343 (2018).

9. Center for Drug Evaluation and Research. Alzheimer's Disease: Developing Drugs for Treatment Guidance for Industy. *U.S. Food and Drug Administration* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/alzheimers-disease-developing-drugs-treatment-guidance-industy (2020).

10. Center for Drug Evaluation and Research. Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products. *U.S. Food and Drug Administration* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enrichment-strategies-clinical-trials-support-approval-human-drugs-and-biological-products (2019).

11. Post, B., Merkus, M. P., de Bie, R. M. A., de Haan, R. J. & Speelman, J. D. Unified Parkinson's disease rating scale motor examination: are ratings of nurses, residents in neurology, and movement disorders specialists interchangeable? *Mov. Disord. Off. J. Mov. Disord. Soc.* **20**, 1577–1584 (2005).

12. Lewis, S. J. G. *et al.* Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach. *J. Neurol. Neurosurg. Psychiatry* **76**, 343–348 (2005).

13. Tan, C. H. & Desikan, R. S. Interpreting Alzheimer disease polygenic scores. *Ann. Neurol.* **83**, 443–445 (2018).

14. outsourcing-pharma.com. Natural history studies 'essential' for rare disease drug development. *outsourcing-pharma.com* https://www.outsourcing-pharma.com/Article/2019/07/17/Natural-history-studies-essential-for-rare-disease-drug-development.

15. Bloem, B. R., Okun, M. S. & Klein, C. Parkinson's disease. *The Lancet* **397**, 2284–2303 (2021).

16. Governor Baker Signs Law Strengthening Alzheimer's and Dementia Treatment in Massachusetts | Mass.gov. https://www.mass.gov/news/governor-baker-signs-law-strengthening-alzheimers-and-dementia-treatment-in-massachusetts.

17. Why early diagnosis is important - Dementia - SCIE. https://www.scie.org.uk/dementia/symptoms/diagnosis/early-diagnosis.asp.

18. Nicholas, L. H., Langa, K. M., Bynum, J. P. W. & Hsu, J. W. Financial Presentation of Alzheimer Disease and Related Dementias. *JAMA Intern. Med.* **181**, 220–227 (2021).