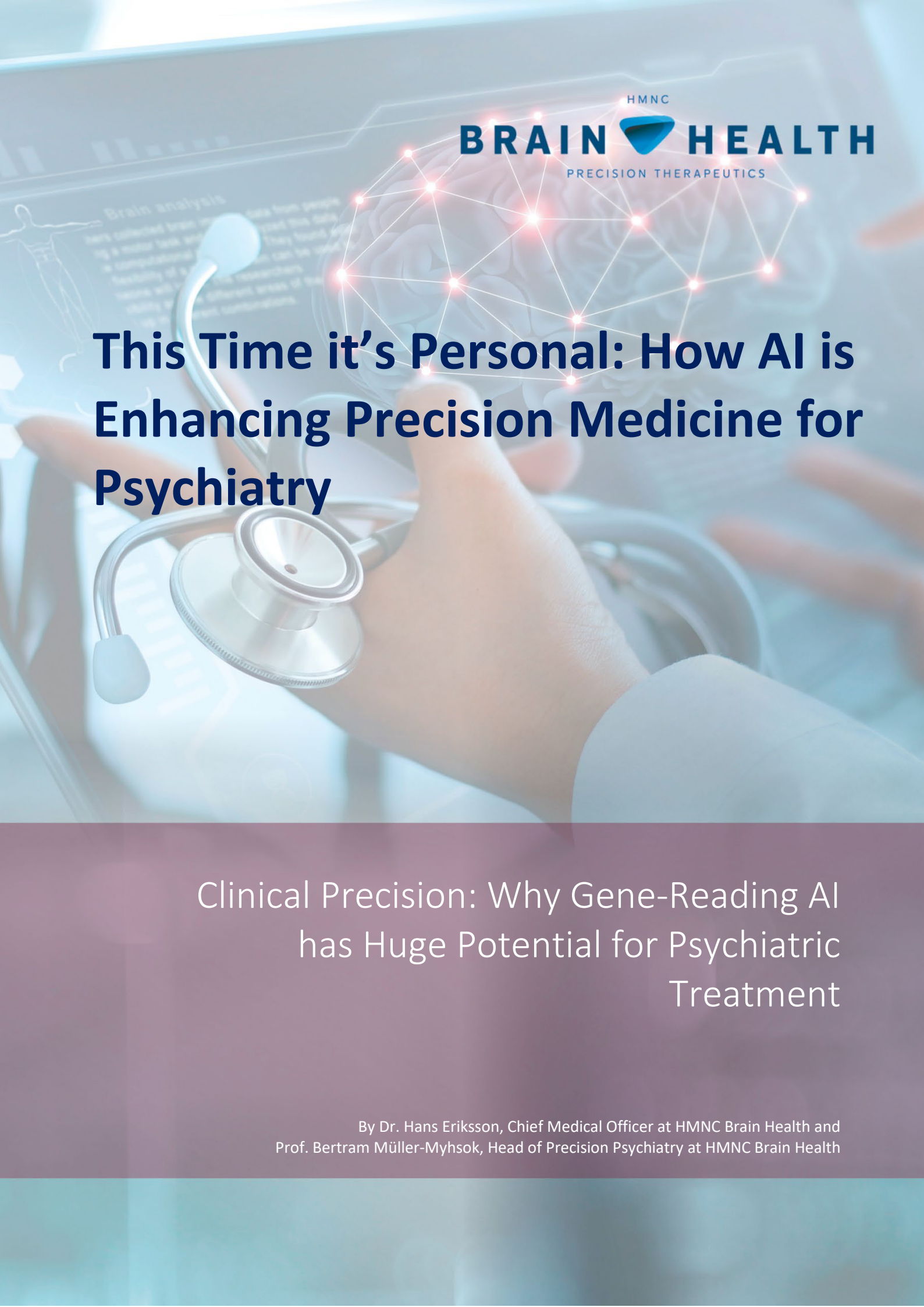

HMNC BRAIN HEALTH
PRECISION THERAPEUTICS

This Time it's Personal: How AI is Enhancing Precision Medicine for Psychiatry

Clinical Precision: Why Gene-Reading AI has Huge Potential for Psychiatric Treatment

By Dr. Hans Eriksson, Chief Medical Officer at HMNC Brain Health and
Prof. Bertram Müller-Myhsok, Head of Precision Psychiatry at HMNC Brain Health

Adapting the tried and tested from oncology to psychiatry

Cancer affecting humans takes more than 100 forms, and the disease has an even longer list of environmental, lifestyle and genetic causes. Despite this, cancer treatment has been a 'one size fits all' process for several decades. Patients typically endured surgery to remove their tumor, followed by several rounds of chemotherapy or radiation to kill cancer cells. Without any insight into their patients' individual genes and specific disease, it was the best that oncologists could do.

Thanks to rapid advances in genomic medicine, that is starting to change. The most promising cancer drugs in development today have a foil called a companion diagnostic, an in vitro test that drills down into a patient's DNA. That allows clinicians to quickly diagnose if a tumor has a specific gene change or biomarker, and determine if the drug is suitable for their patient. It promises to transform cancer treatment from a conveyor belt into an exercise in precision and personalization.

Psychiatry has lagged oncology in terms of more precise and personalized treatment. That is principally because the lack of physiological biomarkers in the field makes diagnosis extremely difficult. The heterogeneity and multimorbidity of psychiatric diseases only add to that challenge. And while certain branches of science and technology have made huge strides in recent years, humans are nowhere near unravelling the scientific mystery of the brain. Neuroscientists still do not understand the brains of small invertebrates that contain a few hundred neurons, let alone the full organ, which has around 100 billion nerve cells.

Against the stacked odds, psychiatry is starting to catch up. Researchers had long wondered why certain patients saw great benefit from their medications for severe depression, anxiety and schizophrenia, whereas others saw none. They began working with pharmaceutical firms like HMNC Brain Health, leveraging genomic breakthroughs to produce highly personalized therapies that are a world away from 'one size fits all.' These therapies, which harness sophisticated biomarker analysis, break down the usual boundaries to define patient groups that will respond particularly well, less well, or not at all to a recommended drug, despite having the same diagnosis.

At HMNC Brain Health, we are enhancing these novel approaches to diagnosing and treating neuropsychiatric disorders with computational approaches, including state-of-the-art Artificial Intelligence (AI). We are developing advanced machine learning algorithms and neural networks that can identify individuals who have a hyperactive stress hormone axis, a subset of patients that makes up around one-third of a depressed cohort.

Our algorithms are highly complex, but our aims are very simple. Giving clinicians the tools to efficiently predict which individuals suffer from a misfiring stress axis will enhance diagnostic confidence, expedite treatment, and ultimately improve outcomes for some of the world's most severely depressed patients.

Background to research and development

Precision and personalization go to the heart of HMNC Brain Health's strategy. Our company's inspiration stems from oncology, and we keep close tabs on cutting-edge approaches in cancer treatment. We have for instance studied how oncologists discover certain variations in an individual's epidermal growth factor receptor (EGFR) gene, to prescribe EGFR inhibitors to the

patient. That is why our main development programs all explore which disease mechanism is involved in the development of depression in individuals, and which specific pharmacological mechanism is most suitable for treating their depression. This allows for the selected use of antidepressants specifically targeting the disease mechanism.

One of our main programs involves a vasopressin V1b receptor antagonist with the internal compound code 'BH-200'. This antidepressant medication has already shown efficacy in a substantial Phase II study conducted by Sanofi. This efficacy may not have been notably superior to any standard, widely used, off-patent antidepressants on the market today, but our trials are breaking new ground with BH-200. We hypothesize that efficacy is driven by a subset of patients who are more responsive to the drug's mechanism of intervention.

This subset of patients appears to suffer from a disturbance in their body's stress hormone system, which is related to the brain's control of the production of cortisol. The brain regulates this cortisol by sending signals along the body's hypothalamus-pituitary-adrenals (HPA) axis, or 'stress axis'. For most people, that stress axis works smoothly. But that is not the case for some severely depressed individuals. In fact, the axis appears to be in a hyperactive mode, and cannot be calmed.

The 'traditional' approach to identifying this subset of patients relies on a physiological test, in which clinicians use both synthetic and naturally occurring hormones that regulate the stress axis. But such physiological tests have failed to gain much traction as a clinical tool, because they are costly, time-consuming, and painstaking procedures that require highly specialized facilities and professionals. In the protocol for the physiological test, the patient ingests oral medication, and then undergoes several rounds of blood sampling, all over a 36-hour period.

HMNC Brain Health's genetic test is carried out via a simple blood sample and checks to see if the patient shares the same genetic signature – or DNA variations – as individuals who have already been diagnosed with irregular stress hormone axes. Carrying this genetic signature should be a strong predictor of responsiveness to the BH-200 antidepressant.

This genetic test is more efficient, and also yields more valuable clinical information. It drills down into an individual's largely immutable genes, meaning that patients only need a single test in their lifetime. Clinicians can thus draw on the result 'for eternity', tailoring treatment if and when the patient suffers a depressive episode. If scaled, the genetic test also has the potential to be more economic than the physiological approach. The genetic test does not just expedite treatment for subset of patients who test positive for the genetic signature; it frees up those who test negative to pursue alternative avenues.

Gene-reading AI

But clinicians do not need to spend hours scrutinizing those genetic tests for the tell-tale signature of hyperactive stress axis. Our algorithms can automatically and instantly identify those variations, thereby predicting the individuals who are most susceptible to treatment.

Our system is just one of several new computational approaches that are bringing precision and personalization into the psychiatry arena. Organizations such as the Psychiatric Genomics Consortium are also identifying more reliable predictors of genomic comorbidities from hard data. Researchers are applying deep learning approaches to epigenetics to better understand the

impact of behavior and environment on the workings of human genes. Scientists are also feeding genetic information about patients into the machine learning algorithms that analyze MRI scans of the brain to generate new insights about an individual's psychiatric disease.

HMNC Brain Health is focusing on a field of AI called probabilistic modelling, which harnesses mathematical approaches such as Bayesian optimization, data compression and automatic model discovery. Right now, our cloud-based AI analyzes a small group of single nucleotide polymorphisms ('SNPs'), the genomic variants at a single base position in the DNA, for the patterns that might betray hyperactive stress axis. Those algorithms have already been trained on a dataset containing nearly 1,000 sets of SNPs. It takes just a few seconds for the AI to infer patterns and output a prediction of the patient's susceptibility to treatment.

We are still in a proof-of-concept stage with our next-generation sequencing method, so we expect the occasional false positive and negative, and are confident these will be ironed out as the algorithms continue to learn. But we are pleased with initial results. It currently takes around four days to carry out the AI-enhanced genetic tests, but the further optimization of datasets, tuning of our algorithms, and wider adoption of the technology will significantly reduce the readout wait.

In the short-term, we plan to feed our system with supplementary data about treatment, trials and readouts, which will bolster its reliability and replicability. Another goal is training the AI to define the sensitivity and specificity of hyperactive stress disorder once it has identified the disease's genetic footprint. We can also train the AI with more dynamic real-world data, such as RNA, proteins, and digital biomarkers from wearables. Our bridging studies in our clinical development programs will be a rich source of data in this respect. Over the longer term, we expect our approach will be applicable for other psychiatric diseases that are caused by a hyperactive stress axis, such as different types of depression, burnout and somatic disorders.

We are also committed to building 'explainable AI', in which the workings and outputs of algorithms are easily intelligible to the clinicians applying them. That will be a crucial factor to accelerating the development and rollout of such computational approaches. If physicians have the tools to carry out multiple tests at the point-of-care, there is potential to obtain results in one day, or even a few hours, in the manner of polymerase chain reaction (PCR) tests for COVID-19.

That would achieve something that was unimaginable just a few years ago: Incorporating precision and personalization into everyday psychiatric treatment.