NETRAMARK

NetraMark's Generative AI Discovers Novel Rare Disease Drug Targets and Unique Patient Subpopulations That Could Substantially Improve Clinical Trial Success Rates

— Newly peer-reviewed, published research demonstrates the power of NetraAI to detect novel and known potential therapeutic targets for amyotrophic lateral sclerosis (ALS) that were not identified using other AI-based methods —

— NetraAI identified well-defined subpopulations that could improve ALS clinical trial outcomes. These results were derived from 116 patients, demonstrating the unique power of the platform compared with other AI methods that required large data inputs —

TORONTO, Jan. 16, 2024 /CNW/ - **NetraMark Holdings Inc. (the "Company" or "NetraMark")** (CSE: AIAI) (OTCQB: AINMF) (Frankfurt: 8TV) a generative AI software leader in clinical trial solutions, announces the publication of new peer-reviewed research that adds to the growing body of evidence supporting the power of its NetraAI solution to provide unique insights into disease biology and identify well-defined patient subpopulations that drive clinical trial success. The data, which appears in the current issue of *Frontiers in Computational Neuroscience*, identified several genes that shed light into ALS pathophysiology and represents new avenues for treatment. The analysis also identified subpopulations of ALS patients based on disease onset.

"These data and related insights underscore the differentiated capabilities of NetraAI compared with other AI-based solutions for target discovery and clinical trial analytics," said Joseph Geraci, PhD, CTO, CSO, Director and Co-Founder, NetraMark, and first author on the publication. "Using a small ALS dataset and a unique machine learning paradigm, we have not only validated previously reported ALS drug targets but also uncovered critical insights into ALS heterogeneity. A major problem with state of the art AI methods for understanding patient populations is that they lack the ability to be critical of how the data is labeled. People are very complex systems, and the NetraAI system is specifically geared to uncover aspects of patient populations that go beyond human observation and expose various driving factors behind the biology of the disease. This technology provides our company with unique insights into how people are truly being affected by a disease and has the potential to enable our clients to significantly improve clinical trial outcomes."

In this study, NetraAI, a unique machine learning (ML) environment, was used to analyze data collected by Answer ALS, the largest collaborative effort in ALS, bringing together multiple research organizations and key opinion leaders. Over 800 ALS patients and 100 healthy controls from eight neuromuscular clinics distributed across the United States were enrolled in this project. NetraAI was made available to medical experts at the Gladstone Institute, allowing them to interact with the ML-generated hypotheses and to evaluate the findings and examine the causal factors that the NetraAI model suggested. This approach bridges a critical gap that exists between advanced ML techniques and human medical expertise.

In contrast with other AI-based methods for analyzing this data set, NetraAI is uniquely engineered to include focus mechanisms that separate small datasets into explainable and unexplainable subsets. Unexplainable subsets are collections of patients that can lead to suboptimal overfit models and inaccurate insights due to poor correlations with the variables involved. The NetraAI uses the explainable subsets to derive insights and hypotheses (including factors that influence treatment and placebo responses, as well as adverse events) that can significantly increase the chances of a

clinical trial success. State of the art AI methods lack these focus mechanisms and assign every patient to a class, even when this leads to "overfitting" which drowns out critical information that could have been used to improve a trial's chance of success.

"One of NetraAI's most powerful features is its ability to gain insights from every element of a clinical data set," said NetraMark President, Josh Spiegel. "This enables a new approach to designing more focused and tailored clinical trials that have a higher likelihood of success and supports the development of personalized therapies tailored to address the specific biology of defined patient populations. This is especially important in complex diseases, such as ALS, that have multiple factors driving disease development, progression, and severity, as well as response to therapy. This publication is further evidence that NetraAI is an impactful solution for improving the biopharmaceutical industry's 88 percent clinical trial failure rate."

Key findings from the study include:

- NetraAI replicated ALS drug targets identified using other analytic methods, but also identified several genes belonging to the same gene family as those previously reported as well as wholly novel targets.
- NetraAI uncovered several targets that may shed light into ALS pathophysiology and treatment efforts. These targets can be grouped into a collection of target classes based on unique ALS-related characteristics, including inflammation, epigenetic, heat shock, neuromuscular junction, autophagy, apoptosis, axonal transport, and excitotoxicity.
- Application of NetraAI to a dataset consisting of 31 bulbar onset and 85 limb onset ALS patients identified distinct subpopulations, each defined by a specific set of driving genes:
    - A subpopulation of 13 limb onset ALS patients was identified to be characterized by an elevated expression of IL200RA and LRRC23.
    - A distinct subpopulation of 11 bulbar onset ALS patients was characterized by a decreased expression of TBC1D20, and an elevated expression of TMEM14A. These genes are biologically connected to TDP-43, which is currently at the forefront of ALS research. NetraMark intends to examine and develop additional insights gleaned from these findings, which are not included in the publication, with the goal of leveraging them to improve the success of future ALS trials.
    - The remaining limb onset patients, which comprised the majority of the dataset, were characterized by expression patterns opposite to the bulbar subpopulation –specifically increased expression of TBC1D20, ALG3P1, CROCC2, AC109439.1, FAM151A, and NKX2101-AS1, and decreased expression of TMEM14A.
- These findings identify specific genetic factors with the potential to accurately define novel subtypes of bulbar and limb-initiated ALS for improved personalized medicine approaches.
- Identification of these subpopulations has significant potential to improve clinical trial outcomes by matching therapeutic interventions to patient disease mechanisms.

About NetraMark
NetraMark is a company focused on being a leader in the development of Generative Artificial Intelligence (Gen AI)/Machine Learning (ML) solutions targeted at the Pharmaceutical industry. Its product offering uses a novel topology-based algorithm that has the ability to parse patient data sets into subsets of people that are strongly related according to several variables simultaneously. This allows NetraMark to use a variety of ML methods, depending on the character and size of the data, to transform the data into powerfully intelligent data that activates traditional AI/ML methods. The result is that NetraMark can work with much smaller datasets and accurately segment diseases into different types, as well as accurately classify patients for sensitivity to drugs and/or efficacy of treatment.

For further details on the Company please see the Company's publicly available documents filed on the System for Electronic Document Analysis and Retrieval (SEDAR).

Forward-Looking Statements
This press release contains "forward-looking information" within the meaning of applicable Canadian securities legislation including statements regarding the Company's objectives with NetraAI, the potential impact of NetraAI on the Company's and its clients' business, the Company's ability to successfully implement its business strategy with NetraAI and the potential improvements arising from NetraAI which are based upon NetraMark's current internal expectations, estimates, projections, assumptions and beliefs, and views of future events. Forward-looking information can be identified by the use of forward-looking terminology such as "expect", "likely", "may", "will", "should", "intend", "anticipate", "potential", "proposed", "estimate" and other similar words, including negative and grammatical variations thereof, or statements that certain events or conditions "may", "would" or "will" happen, or by discussions of strategy. Forward-looking information includes estimates, plans, expectations, opinions, forecasts, projections, targets, guidance, or other statements that are not statements of fact. The forward-looking statements are expectations only and are subject to known and unknown risks, uncertainties and other important factors that could cause actual results of the Company or industry results to differ materially from future results, performance or achievements. Any forward-looking information speaks only as of the date on which it is made, and, except as required by law, NetraMark does not undertake any obligation to update or revise any forward-looking information, whether as a result of new information, future events, or otherwise. New factors emerge from time to time, and it is not possible for NetraMark to predict all such factors.

When considering these forward-looking statements, readers should keep in mind the risk factors and other cautionary statements as set out in the materials we file with applicable Canadian securities regulatory authorities on SEDAR at www.sedar.com including our Management's Discussion and Analysis for the year ended September 30, 2022. These risk factors and other factors could cause actual events or results to differ materially from those described in any forward-looking information.

The CSE does not accept responsibility for the adequacy or accuracy of this release.

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