NETRAMARK'S AI-BASED CLINICAL SOLUTION IDENTIFIES NOVEL LUNG AND COLON CANCER BIOMARKERS AND PATIENT SUBPOPULATIONS

— Insights open the door for potential precision immunotherapy innovation targeting novel pathways and patient enrichment strategies with the potential to improve clinical trial success rates —

TORONTO, April 10, 2024 /CNW/ - **NetraMark Holdings Inc. (the "Company" or "NetraMark")** (CSE: AIAI) (OTCQB: AINMF) (Frankfurt: 8TV) a generative AI software leader in clinical trial analytics, announces the presentation of new data describing how its proprietary NetraAI clinical trial solution identified novel biomarkers and protein-protein interaction (PPI) pathways associated with specific forms of non-small cell lung cancer (NSCLC) and colorectal cancer (CRC) using small data sets and a self-learning algorithm that obviates the need for large training data sets. These insights, or NetraPerspectives, have the potential to advance the personalized medicine landscape through patient enrichment strategies while also enabling novel diagnostic and therapeutic avenues, enhancing patient care and outcomes in these complex indications. Dr. Joseph Geraci, PhD, Founder and Chief Scientific Officer of NetraMark, presented the data yesterday in two posters at the American Association of Cancer Research (AACR) Annual Meeting 2024, which is taking place April 5-10, 2024 in San Diego, California.

"These findings add to the growing body of evidence demonstrating that NetraAI can extract meaningful insights from small datasets, offering an alternative approach to stratify patients while not reinforcing our current knowledge and belief biases about patient populations," said Dr. Geraci. "NetraAI's ability to identify variables that define specific patient personas with high statistical significance has the potential to advance current research paradigms and patient-specific treatments contributing to precision medicine, that help patients receive the most effective care based on their specific genetic make-up and disease etiology. We believe that NetraAI will be especially valuable in the development and clinical use of precision oncology medicine given the heterogeneous and complex alterations to genes and signaling pathways that impact the development and progression of cancer as well as response to therapy."

Both posters were presented in the "Late-Breaking Research: Bioinformatics, Computational Biology, Systems Biology, and Convergent Science 2" session, which took place yesterday.

 The poster titled "
[NetraAI-driven discovery of novel biomarkers in MSI-high colon cancer for precision immunotherapy](#)"
(Abstract #LB395) describes the use of Attractor AI algorithms to identify causal clusters of variables (hypotheses) that explain specific sub-populations of patients with microsatellite instability-high (MSI-H) CRC. MSI-H tumors are characterized by an extensive mutational load, which fosters the production of neoantigens and amplifies immune visibility, making them prime candidates for immunotherapy. However, these same factors contribute to heterogeneity that further complicates the efficacy of targeted therapies. NetraAI was applied to a data set consisting of tens of thousands of RNA expression variables from 390 samples from CRC patients. These profiles included 44 MSI-H and 21 MSI-low (MSI-L) samples and the dataset used consisted of a total of 22,283 variables. Key findings from the analysis include:

- In one NetraPerspective, there was a MSI-H subpopulation identified, consisting of 29 MSI-H and 2 MSI-L samples. This subpopulation is characterized by expression of CATSPERB (p=1.2 x 10$^-$

^{7}), MLPH ($p=4.9 \times 10^{-5}$), FUT8 ($p=8.6 \times 10^{-5}$), DUSP4 ($p=1.1 \times 10^{-3}$), and PLLP ($p=0.01$).

- Constructing PPI networks based on the identified variables suggests a complex interplay among them, particularly in the context of spermatogenesis.
  - Mismatch repair (MMR) is essential for ensuring genetic integrity during sperm production. The findings of the NetraAI analysis suggest that defects in MMR play a causal role in the genetic instability seen in MSI-H CRC.
- The specificity of CATSPERB to an MSI-H colon cancer subgroup posits it as a potential biomarker for identifying patients who might benefit from tailored therapeutic approaches, contributing to the personalized medicine landscape.
  - CATSPERB protein is primarily associated with calcium channels in sperm, but its over-expression in a subset of MSI-H CRC patients suggests that the protein may modulate calcium signaling in tumor cells, which is known to play a role in a variety of cellular processes that drive cancer cell proliferation, survival, and metastasis.

The poster titled "
[The power of NetraAI: Precision medicine in oncology through sub-insight learning from small data sets](#)
" (Abstract #LB396) describes the use of Attractor AI algorithms to identify variables defining specific subpopulations of patients with NSCLC. A small data set consisting of 104 gene expression samples of adenocarcinoma (ADC) and squamous cell carcinoma (SSC) was compiled from two NSCLC datasets. Key findings from the analysis include:

- One NetraPerspective showed multiple explainable subpopulations of NSCLC, primarily stratified as ADC or SCC subpopulations. Interestingly, there were multiple subpopulations of each subtype suggesting that different combinations of variables drive specific ADC and SCC subtypes.
- Examination of each subpopulation using NetraAI's unique zoom capabilities of NetraAI, identified the specific patients and characterizing variables.
  - In one NetraPerspective, NetraAI distinguished between ADC and SCC subtypes through unique genetic signatures, with 9 out of 10 variables correlating with known NSCLC markers. This validates the methods and technology used by NetraAI.
- PIGX emerged as a novel target due to its previously unexplored role in cancer biology.
- Further investigation into PPI networks revealed a significant connection between PIGX and BACE1, a protein implicated in NSCLC brain metastasis. This opens new avenues for understanding molecular mechanisms underlying cancer progression and metastasis.
- PIGX is also related to PIGN which is associated with genomic instability and regulates spindle assembly checkpoint proteins in leukemia transformation and progression.

"The demand for personalized oncology treatment strategies necessitates novel AI/ML technologies that can leverage smaller or limited datasets to uncover actionable insights," added Dr. Geraci. "In refining patient stratification and subtype discrimination, NetraAI overcomes the challenges inherent in conventional methods that depend on large datasets. This approach has the potential to identify novel oncology therapeutic targets and improve the success rate of clinical trials in cancer indications that have significant unmet need."

About NetraAI

In contrast with other AI-based methods, 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. Other 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.

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 potential value of the Company's technology to identify biomarkers, novel oncology therapeutic targets and patient subpopulations with statistical significance with the potential to use to de-risk clinical trials, advance research paradigms and develop personalized medicine 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.sedarplus.ca including our Management's Discussion and Analysis for the year ended September 30, 2023. 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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