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PERSONAL GENOME DIAGNOSTICS' EXOME ANALYSIS AND CANCER BIOLOGY EXPERTISE IS ENABLING ADVANCES IN GENOME-BASED CANCER THERAPY

—Study in Nature Genetics Used PGDx Exome Analysis to Identify Previously Unknown Mutation with Potential as New Drug Target for Lethal Childhood Brain Cancer—
—National Cancer Institute (NCI) Study Published in Science Used PGDx Exome Sequencing to Identify Epithelial Cancer Antigens with Demonstrated Immunotherapy Potential—
—Study in Clinical Cancer Research Used PGDx Exome Analysis in Tandem with Avatar Models of Breast Cancer to Guide Personalized Treatment—

BALTIMORE, MD, June 10 2014 – Personal Genome Diagnostics Inc. (PGDx), a provider of advanced cancer genome analysis and testing services, reported that its exome analysis services played a central role in several cancer studies recently published in leading scientific journals. PGDx's exome analysis incorporates the company's proprietary technology and its scientists' deep understanding of the genomics and biology of cancer.

The studies detected a previously unknown brain cancer mutation with potential as a new drug target, identified epithelial cancer antigens that have shown promise as targets for immunotherapy, and detected breast cancer mutations that were used with an avatar model of the patient's cancer to guide personalized treatment.

Antony Newton, chief commercial officer of PGDX, commented, "The diversity of these studies illustrates the expanding power and utility of our exome analysis services, and they confirm that PGDx is very skilled at zeroing in on bona fide cancer mutations from large data sets, a prerequisite for this type of research. Our scientists bring exceptional expertise to exome analysis, having helped pioneer the approach, and they combine that expertise with a deep understanding of the biology of cancer. Their ability to make connections between multiple data sources also helped produce the discoveries reported in all three studies."

Siân Jones, PhD, a study co-author and director of genome analyses at PGDx, added, "In the brain cancer study, we collaborated with Duke Medicine and scientists from Chinese research institutions to identify a previously unknown mutation that may have potential as a target for new drug development. The groundbreaking NCI-sponsored study led by Dr. Steven Rosenberg was the first time that exome sequencing has been successfully used to identify cancer antigens with demonstrated utility for immunotherapy. The third study was the first ever to show a positive impact on patient outcomes from the use of a live avatar model of the patient's own cancer. It confirmed that combining exome sequencing with other personalized medicine approaches has the potential to enhance therapeutic decision making."

Dr. Jones, further noted, "The success of all three projects was largely dependent on our ability to identify real mutations from noise, based on our extensive experience in using matched normal DNA to differentiate germline polymorphisms from real somatic mutations in whole genome, exome and targeted analyses. While many believe it is feasible to accomplish this using a normal reference, this less rigorous approach limits the potential to discover new somatic alterations, resulting in suboptimal results and a failure to advance our understanding of the genomics of cancer."

The brain cancer study recently published in the online edition of *Nature Genetics*[1] was a collaborative effort to better understand brainstem glioma, a deadly form of brain cancer that strikes children and young adults. A key finding was the identification by PGDx of a previously unknown mutation present in the PPM1D gene, which stimulates cell growth and proliferation. This mutation was not previously associated

with brainstem glioma, and it is not seen in other brain tumors. PGDx scientists used exome sequencing to discover the new mutation and help elucidate its role. PPM1D represents a promising target for the development of new drugs to treat this lethal disorder.

Senior author Hai Yan, MD, PhD, noted, “A major challenge of this study was to accurately identify the few critical mutations out of a large of number of potential candidates. We selected PGDx for their state-of-the-art genetic analysis tools and expertise in connecting the genetics to the biology of cancer.”

In the second study, published in *Science*[2] in May, researchers at NCI led by Dr. Steven Rosenberg used PGDx’s whole exome sequencing to demonstrate that the immune system can mount an endogenous T-cell immune response against a mutation expressed by an epithelial cancer, and that this response can be harnessed for therapeutic benefit. PGDx scientists conducted whole exome sequencing that identified epithelial cancer mutations that had antigenic potential. The NCI team then generated a therapeutic product enriched with T-cells that were highly reactive to these mutations. In early testing, the therapy had a positive therapeutic impact in a number of patients with epithelial cancer, which accounts for about 90% of cancer deaths in the U.S.

The third study, which appeared in *Clinical Cancer Research*[3] in March, summarizes early experience in developing personalized cancer treatments by integrating data from PGDx’s exome sequencing analyses with data from avatar mouse models, developed from the patient’s own tumor. All the tumor samples profiled by PGDx contained biologically or clinically meaningful genomic alterations, and some of these were used to optimize treatment via functional testing in the avatar. This study demonstrated the feasibility of the approach, with 57% of patients receiving personalized therapy and 77% of those experiencing a clinical benefit from the tailored treatment.

Senior author Dr. Manuel Hidalgo, commented, “In this study we wanted to combine a highly comprehensive exome sequencing approach with bench testing of therapies in animal models. Working with PGDx gave us access to the most advanced technology approaches combined with interactions with a team of experienced scientists, and this really helped us understand the tumor biology.”

[1] Exome sequencing identifies somatic gain-of-function PPM1D mutations in brainstem gliomas, Liwei Zhang, Lee H Chen, Hong Wan, Rui Yang, Zhaohui Wang, Jie Feng, Shaohua Yang, Sian Jones, Sizhen Wang, Weixin Zhou, Huishan Zhu, Patrick J Killela, Junting Zhang, Zhen Wu, Guilin Li, Shuyu Hao, Yu Wang, Joseph B Webb, Henry S Friedman, Allan H Friedman, Roger E McLendon, Yiping He, Zachary J Reitman, Darell D Bigner, Hai Yan, *Nature Genetics*, Advance Online Publication, DOI: 10.1038/ng.2995.

[2] Cancer Immunotherapy Based on Mutation-Specific CD4+ T Cells in a Patient with Epithelial Cancer, Eric Tran, Simon Turcotte, Alena Gros, Paul F. Robbins, Yong-Chen Lu, Mark E. Dudley, John R. Wunderlich, Robert P. Somerville, Katherine Hogan, Christian S. Hinrichs,Maria R. Parkhurst, James C. Yang, Steven A. Rosenberg, *Science*, 9 May 2014, Vol 344; 642-645

[3] Integrated Next-Generation Sequencing and Avatar Mouse Models for Personalized Cancer Treatment, Elena Garralda, Keren Paz, Pedro P. López-Casas, Siân Jones, Amanda Katz, Lisa M. Kann, Fernando López-Rios, Francesca Sarno, Fátima Al-Shahrour, David Vasquez, Elizabeth Bruckheimer, Samuel V. Angiuoli, Antonio Calles, Luis A. Diaz, Victor E. Velculescu, Alfonso Valencia, David Sidransky, Manuel Hidalgo*, Clinical Cancer Research;* 20(9); 2476–84.

About Personal Genome Diagnostics

Personal Genome Diagnostics (PGDx) provides advanced cancer genome analyses to oncology researchers, drug developers, clinicians and patients. The company uses advanced genomic methods and its deep expertise in cancer biology to identify and characterize the unique genomic alterations in tumors. PGDx’s proprietary methods for genome sequencing and analysis are complemented by its extensive experience in cancer genomics and clinical oncology. The founders of PGDx, Luis Diaz, MD, and Victor Velculescu, MD, PhD, are internationally recognized leaders in cancer genomics at Johns Hopkins University who have extensive experience in the practical application of advanced genomic technologies to drug development and clinical practice. PGDx’s CLIA-certified facility provides personalized cancer genome analyses to patients and their physicians. For more information, visit www.personalgenome.com.

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