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TGen-US Oncology data guides treatment of metastatic triple-negative breast cancer patients

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Genomic sequencing has revealed therapeutic drug targets for difficult-to-treat, metastatic triple-negative breast cancer (TNBC), according to an unprecedented study by the Translational Genomic Research Institute (TGen) and US Oncology Research.

The study is published by the journal Molecular Cancer Therapeutics and is currently available online.

By sequencing, or spelling out, the billions of letters contained in the genomes of 14 tumors from ethnically diverse metastatic TNBC patients, TGen and US Oncology Research investigators found recurring significant mutations and other changes in more than a dozen genes. In addition, the investigators identified mutations previously unseen in metastatic TNBC and took the sequencing data into account in selection of therapeutic protocols specific to each patient's genetic profile.

"This study stands as a one-of-a-kind effort that has already led to potentially beneficial clinical trials, and sets the stage for future investigations," said Dr. John Carpten, Ph.D., TGen's Deputy Director of Basic Science and Director of TGen's Integrated Cancer Genomics Division, and the study's senior author.

The most frequently mutated gene among the tumors (seven of 14) was the TP53 tumor suppressor, and aberrations were observed in additional

tumor suppressor genes including CTNNA1, which was detected in two of six African American patients (who typically have more aggressive and treatment-resistant disease). Alterations were also seen in the ERBB4 gene, known to be involved in mammary-gland maturation during pregnancy and lactation, but not previously linked to metastatic TNBC.

The study included an "outlier analysis," which assessed expression patterns for each tumor when compared against the other tumors examined in the study. Specific cancer genes overexpressed among tumors in the study's cohort included: ALK, AR, ARAF, BRAF, FGFR2, GLI1, GLI2, HRAS, HSP90AA1, KRAS, MET, NOTCH2, NOTCH3, and SHH. Significantly underexpressed cancer genes included: BRCA1, BRCA2, CDKN2A, CTNNA1, DKK1, FBXW7, NF1, PTEN, and SFN.

Each tumor was genomically unique, but nine of the 14 contained alterations in one or both of two particular cellular pathways: RAS/RAF/MEK/ERK and PI3K/AKT/MTOR. Targeted therapeutic intervention aimed at these pathways achieved impressive responses in several cases.

"Importantly, the analysis provided insights into the potential unique therapeutic vulnerabilities of each cancer," said Dr. Joyce O'Shaughnessy, M.D., the study's other co-lead author. Dr. O'Shaughnessy is a practicing oncologist with Texas Oncology—an affiliate of The US Oncology Network—and is the Celebrating Women Chair of Breast Cancer Research at Baylor Charles A. Sammons Cancer Center.

Metastatic TNBC is a highly aggressive form of breast cancer that disproportionately affects African-Americans. It is called triple-negative because tumors do not express the estrogen receptor, progesterone

receptor or HER-2, the biomarkers successfully targeted in most breast cancers.

Metastatic TNBC also has a poor prognosis once the cancer has spread to other organs, with a median survival rate among metastatic patients of only one year. While TNBC accounts for only about 15 percent of all breast cancers, its more aggressive biology makes it responsible for nearly one in four deaths related to this disease.

"The nature of this disease cries out for innovative research techniques such as whole genome sequencing coupled with new tools for data analysis," said Dr. David Craig, Ph.D., TGen's Deputy Director of Bioinformatics, and one of the study's co-lead authors.

"We are aware that these results are preliminary and based on a small series of patients," said Carpten. "However, our study will pave the way for new clinical trials and novel hypotheses for future testing in a very difficult to treat cancer."

Whole-genome sequencing of tumors and normal tissue was performed on Life Technologies Corporation's Applied Biosystems SOLiD™ 4.0 platform, and results were validated in a CLIA-certified laboratory.

Provided by The Translational Genomics Research Institute