PLOS ONE Study Finds HIV Genotypic Sequencing Test Performs Comparably to Standard Phenotypic Test in Predicting Potential Response to CCR5 Antagonist

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Genotypic HIV tropism laboratory-developed testing service now available nationally for HIV-infected patients

MADISON, N.J., Oct. 2, 2012 /PRNewswire/ -- A laboratory-developed blood test that uses deep-sequencing technology performed comparably to the industry's standard phenotypic test in helping to predict potential clinical response to HIV-1 antiretroviral CCR5-antagonist therapy, according to a new study from researchers at Quest Diagnostics (NYSE: DGX) and Pfizer. The findings underscore the potential of advanced sequencing technologies to aid in the cost-effective management of patients infected with HIV using CCR5 antagonists.

The study, "A Genotypic Test for HIV-1 Tropism Combining Sanger Sequencing with Ultradeep Sequencing Predicts Virologic Response in Treatment-Experienced Patients," was published online September 27 in the peer-reviewed, open-access journal PLOS ONE: http://dx.plos.org/10.1371/journal.pone.0046334.

"Phenotyping to identify HIV tropism has played a critical role for the past five years in disease management for thousands of HIV-infected patients in the United States," said study investigator Rick L. Pesano, M.D., Ph.D., medical director, infectious diseases, Quest Diagnostics. "By demonstrating that faster, more cost-effective viral-genomic sequencing performs comparably to phenotypic testing, our study suggests another option for determining HIV tropism, an essential step in determining if a CCR5 antagonist therapy is a potential treatment option."

The study compared the performance of a genotypic laboratory-developed test from Quest Diagnostics to a widely offered phenotypic laboratory test in the United States to determine HIV-1 tropism on patient samples. Tropism refers to the type of cellular co-receptor, CCR5 or CXCR4, through which HIV-1 infects human cells. Viruses that use CCR5 are called R5-tropic ("R5") and those that use CXCR4 are called X4-tropic ("X4"). CCR5 antagonists can reduce HIV-1 viral loads in patients with only R5 virus, but are not recommended in patients with X4 virus or a dual-mixed combination of R5/X4.

Tropism varies by patient, and X4 virus may emerge over time in patients initially infected with R5 virus. Phenotyping examines the ability of the patient's cloned virus to infect cells, while genotypic tests examine the genetic sequence of the patient's virus. Although phenotyping has been the standard tropism detection method in the United States, genotypic tropism tests are widely used and supported by medical guidelines in Europe.

The Quest Diagnostics laboratory-developed test used in the study employed triplicate population sequencing (TPS), which involves genotyping the third variable (V3) loop, a region of the virus that binds to the CCR5 or CXCR4 co-receptor, and bioinformatics, to infer tropism in patients harboring R5, X4 or dual-mixed virus. A highly sensitive test is required to ensure the detection of X4 virus and exclude patients with low levels of X4 virus from receiving CCR5 antagonist therapy. For this reason, if TPS only detected R5 virus, highly sensitive ultradeep sequencing (UDS), which is able to detect minority X4 HIV-1 variants, was performed as a "reflex" test.

Researchers found that the genotypic and phenotypic tests performed comparably at predicting response in patients undergoing therapy with maraviroc. At week eight, the positive predictive value was 66% for the phenotypic test and 65% for the genotypic test, and negative predictive values were 59% for phenotyping and 58% for genotyping.

Quest Diagnostics launched the Quest Diagnostics HIV-1 Tropism with Reflex to Ultradeep sequencing (UDS) laboratory-developed testing service, based on the genotypic-tropism testing technique used in the study, in June 2012. It is the first genotypic-tropism testing service available to physicians in the United States to demonstrate comparable performance to phenotyping in aiding the selection of patients for potential treatment with CCR5 antagonists. The company's laboratory in San Juan Capistrano, California, developed, validated and performs the testing service for clinicians nationally.

Quest Diagnostics can provide results from the testing service in approximately a week for samples with a TPS result of X4 and in as little as 10 days for samples reflexed to UDS, compared to reported turnaround times of approximately 14 days for the phenotyping test used in the study.

"It is gratifying that sequencing has advanced to a level of sophistication that now enables it to perform comparably to phenotyping," said study investigator Ron M. Kagan Ph.D., director of Bioinformatics, Infectious Diseases, for the Quest Diagnostics Nichols Institute, an advanced test research and development center. "Quest Diagnostics has a strong record of innovation in HIV testing, and we look forward to exploring further the potential of genetic sequencing, and UDS in particular, as tools for helping to manage HIV disease in other applications."

Study Strengths and Limitations

The study's strengths include its use of 327 de-identified samples from the MOTIVATE and A4001029 clinical trials, including clinical outcome data, that were part of the data submitted to the FDA for market approval of maraviroc. Although the study was retrospective, its inclusion of de-identified samples from patients from both studies helped to ensure that patients were included in the study who received maraviroc regardless of their viral tropism status, reducing the bias from using samples previously screened with the first commercial phenotyping laboratory test in the U.S. Limitations include the use of specimens from only treatment-experienced patients, although prior studies demonstrate that UDS effectively detects tropism in treatment-naive patients, and the use of algorithms focused on HIV-1 subtype B, which, while found in the vast majority of U.S. HIV-1 infected patients, is less common outside the U.S.

The MOTIVATE and A4001029 protocols were multi-center, multi-investigator studies, approved by institutional review board or independent ethics committee at each study center. Written informed consent was obtained from all participants.

About Quest Diagnostics

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centers, and provides interpretive consultation through its extensive medical and scientific staff. Quest Diagnostics is a pioneer in developing innovative diagnostic tests and advanced healthcare information technology solutions that help improve patient care. Additional company information is available at QuestDiagnostics.com. Follow us at Facebook.com/QuestDiagnostics and Twitter.com/QuestDX.

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