Molecular Pathology Selected Abstracts, 6/16

Editors: Donna E. Hansel, MD, PhD, chief, Division of Anatomic Pathology, and professor, Department of Pathology, University of California, San Diego; John A. Thorson, MD, PhD, associate professor of pathology, director of the Clinical Genomics Laboratory, Center for Advanced Laboratory Medicine, UCSD; Sarah S. Murray, PhD, professor, Department of Pathology, and director of genomic technologies, Center for Advanced Laboratory Medicine, UCSD; and James Solomon, MD, PhD, resident, Department of Pathology, UCSD.

A novel urine test to detect prostate cancer

Screening for prostate cancer historically has involved digital rectal exam to palpate a nodule and blood tests to measure and track prostate-specific antigen. In recent years, the application of PSA screening for men with prostate cancer has undergone re-evaluation because a proportion of men with elevated PSA are, ultimately, diagnosed with no prostate cancer or clinically insignificant prostate cancer at the time of prostate biopsy. These results have led to the suggestion that PSA screening may result in unnecessary biopsies in a proportion of men. Several groups recently have explored alternative methods to identify clinically significant, high-risk prostate cancer—defined as a Gleason score of 7 or more—with improved specificity and early in the course of disease. And several blood- and urine-based studies have been published, including studies involving the urine-based PCA3 assay, blood-based Prostate Health Index, and four-kallikrein panel. A recent study by the authors expanded on prior research by this group that proposed a candidate gene panel for the early diagnosis of high-risk prostate cancer. In the current study, the authors used whole urine to measure mRNA levels for the candidate genes *HOXC4, HOXC6, DLX1, TDRD1, KLK3,* and *PCA3* and combined these results with the clinical factors of age, PSA level, family history, digital rectal exam findings, and prior biopsy results in order to develop a predictive patient-risk model. The multimodal risk score was developed using a prospective cohort of 519 men, with validation on a second prospective cohort of 386 men recruited from six urology centers. The results showed that urine mRNA testing using reverse transcription quantitative polymerase chain reaction for HOXC6 and DLX1 combined with PSA density and prior negative prostate biopsies could best predict high-risk prostate cancer. In the analysis, patient age, PSA level, and family history did not appear to significantly improve the findings. Applying this test to the prediction of high-risk prostate cancer led to a negative predictive value of 98 percent for a Gleason score of 7 or more and reduced unnecessary biopsies by 53 percent, with the test panel outperforming the competing urine-based PCA3 test. Further validation of this urine-based, non-invasive method for predicting high-risk prostate cancer may prove valuable in better stratifying patients who require prostate biopsies.

Van Neste L, Hendriks RJ, Dijkstra S, et al. Detection of high-grade prostate cancer using a urinary molecular biomarker-based risk score [published online ahead of print April 20, 2016]. *Eur Urol.* doi:10.1016/j.eururo.2016.04.012.

Correspondence: Jack A. Schalken at jack.schalken@radboudumc.nl

[hr]

Detection of activating EGFR alterations in non-small cell lung cancer

In non-small cell lung cancer, response to epidermal growth factor receptor tyrosine kinase inhibitors has been associated with activating alterations in the *EGFR* gene. Approximately 10 to 30 percent of non-small cell lung cancer (NSCLC) cases will have an activating alteration in EGFR frequently caused by deletions or mutations in exon 19 of the *EGFR* gene. Laboratory testing for *EGFR* gene changes is recommended for patients diagnosed with NSCLC, although the methodology used for testing and the sequences tested are determined by individual laboratories. In many cases, focused sequencing of the *EGFR* gene is performed using hotspot PCR-based assays that correspond to the 746-750 amino acid range of the EGFR protein. In this study, the authors used a hybrid

capture-based comprehensive genomic profiling approach to evaluate exon 19 deletions in the *EGFR* gene in patients with NSCLC. This technique, performed on formalin-fixed, paraffin-embedded tissue, used adaptor ligation-based libraries to a mean coverage depth of 678X of a 236 cancer-related genes panel that included EGFR. The results from comprehensive genomic profiling analysis identified exon 19 deletions or mutations in 400 patients, with 96.5 percent of these alterations (386 patients) associated with the commonly altered 746-750 amino acid range of EGFR. However, the remaining 14 patients were found to have deletions involving nearby gene regions that are typically not covered by routine clinical laboratory testing for EGFR, but which also predict response to EGFR tyrosine kinase inhibitors. These deletions corresponded to the 753-761 and 752-759 regions of the EGFR protein, which forms part of the C-helix of the EGFR proteins. The study results were compared to those of routine laboratory testing that had been performed on 77 of the 400 patients. In 71 patients who had the common 746-750 amino acid EGFR alteration range identified by comprehensive genomic profiling, only 59 patients were identified through routine testing. Furthermore, of six patients identified with C-helix EGFR alterations, only one was previously identified by routine laboratory testing. The results of this study suggest that improved validation of existing routine laboratory testing or use of a secondary method of EGFR exon 19 analysis, or both, may help identify lung cancer patients who could respond to EGFR-targeted therapy.

Schrock AB, Frampton GM, Herndon D, et al. Comprehensive genomic profiling identifies frequent drug-sensitive EGFR exon 19 deletions in NSCLC not identified by prior molecular testing [published online ahead of print March 1, 2016]. *Clin Cancer Res.* doi:10.1158/1078-0432.CCR-15-1668.

Correspondence: Vincent A. Miller at vmiller@foundationmedicine.com and Siraj M. Ali at sali@foundation medicine.com