New Multi-Gene Liquid Biopsy Biomarker for Prostate Cancer

BY WARREN FROELICH

With the prostate-specific antigen (PSA) test now considered a less-than-reliable screen for prostate cancer, a worldwide search is under way to find an inexpensive, minimally invasive, and more effective tool to replace what was once considered the gold standard biomarker.

Now, an international team of researchers is reporting the creation of a multi-gene liquid biopsy biomarker or signature with a greater than 90 percent accuracy to diagnose and monitor disease status during treatment.

"There is a significant unmet need for the development of a new biomarker in this space," said Mark Kidd, PhD, Laboratory and Scientific Director with Wren Laboratories who presented the findings during the American Association for Cancer Research (AACR) Virtual Annual Meeting II, held online June 22-24.

"We developed a blood-based gene signature that is more than 90 percent accurate as a diagnostic that is significantly more accurate than PSA," he added. "It can be reduced by surgery and detects biochemical recurrence even in the absence of image-negative disease."

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Added Irvin Modlin, MD, PhD, Emeritus Professor with the Yale University School of Medicine Gastroenterological and Endoscopic Surgery group, who developed the biomarker and is the study's principal investigator: "A liquid biopsy for prostate cancer is far more comfortable (finger prick or venous blood draw) than a histological biopsy, is readily repeatable, and can provide real-time information avoiding the painful and invasive nature of random prostatic biopsy."

Though encouraging, the researchers acknowledge that more work must still be done before their new tool can become an approved and accepted strategy to diagnose and monitor prostate cancer activity during treatment.

"There are several questions that remain to be addressed, including types of prostate cancer that the signature detected and monitored, and whether we are detecting the low and less important prostate cancers or the more aggressive ones," said Jorge S. Reis-Filho, MD, PhD, Chief of Experimental Pathology Service with Memorial Sloan Kettering Cancer, who co-chaired this session for AACR.

"And as for all biomarkers, ulterior validation using prospective clinical trials may be required," he added.

Until about 2008, doctors and professional organizations encouraged yearly PSA screening for men beginning at age 50, with age 45 for those considered at higher risk. However, more recent studies showed that PSA exhibited low specificity and led to overdiagnosis in patients with otherwise benign prostate conditions.

As a result, many patients have undergone often painful biopsies every year used to confirm the presence or absence of the cancer. Further, the PSA test has yielded only a moderate reduction in mortality from prostate cancer. The evolving negative opinion set in motion a global exploration to find new prostate cancer biomarkers that could identify tumors quickly, easily, accurately, and with little or no pain.

Among the list of potential biomarkers now being investigated are nucleotides, including messenger RNA (mRNA) molecules, sloughed off into the blood from tumor cells. Such molecules are considered stable with the potential to serve as disease biomarkers in a liquid biopsy to screen for disease and evaluate treatment options and progress. As envisioned, this blood-based assay also would provide a "real-time window" of tumor activity on the microscopic level, and potentially capture pre-malignant prostate disease.

"We were interested in evaluating prostate cancers throughout their natural history and therefore have focused on developing a tool (mRNA) that can capture the entire spectrum of biological alterations throughout the prostate cancer evolution," Kidd explained.

Study Details

For their study, the research team mined several publicly available transcriptome databases (1,159 samples)—a collection of RNA molecules that's the product of gene expression—using several analyses to identify genes that were upregulated or common to prostate cancer compared to normal blood-based transcriptomes.

Seven prostate cancer cell lines and two normal prostate epithelial lines were used to assess candidate genes. Marker genes were identified in prostate cancer tissue and confirmed in all TCGA-PRAC (prostate adenocarcinoma) dataset samples.

The result was a set of 27 genes—a gene signature or biomarker—that the team subsequently tested for effectiveness as a diagnostic and monitoring tool for the disease. In their initial round of testing, the research team found that expression levels in their 27-gene marker were about 36 times higher in cell lines and prostate cancer tumors than benign prostate conditions and normal controls, with higher numbers based on malignancy.

The team subsequently built an algorithm to model gene expression in blood, which provided a mathematical score for how well the marker differentiated prostate cancer from controls; scores could be used to define disease status (progressive vs. stable), scaled from 0 (lowest risk) to 100 percent (highest).

Among the early tests, the model was used to evaluate three cohorts consisting of blood and tissue samples from 134 prostate cancers, 44 benign prostate conditions such as benign prostatic hyperplasia (BPH), and 55 controls. The researchers also analyzed PSA for accuracy in tumor and blood samples using the same model.

The results showed the 27-gene marker was 92 percent accurate in distinguishing prostate cancer from controls with a sensitivity of 94.4 percent and specificity of 89.95 percent. By comparison, PSA was 48 percent accurate.

With deeper patient analysis, the research team subsequently determined their marker yielded 6.1 percent false positives and 5.7 percent false negatives, or an accuracy of 94 percent, which Kidd said would be "appropriate for screening, disease stratification, and therapeutic monitoring."

"We envision that the identification of a 'positive' score by the PROSTest biomarker will identify men at highest risk for prostate cancer," Kidd added. "This could help in the clinical management by stratifying patients and thereby identifying those in need of further assessment, for example, a biopsy."

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So, what can be done? "I think one of the aspects that we cannot forget is that there are hospitals that take care of minority groups," she explained. "They are disproportionately carrying the burden of this disease. So, providing resources to those hospitals that take care of these patients is key."

Looking to the future, Cruz-Correa emphasized the importance of preventive care and early detection. "Minorities are by far the groups that present with cancer at advanced stage," she said. "It's usually a direct response to simply not having the right test at the right time. So, we need to go back to cancer screening and prevention."

Ongoing health disparity research is vital to improving outcomes for these patients, and as mentioned above, this underscores the need for equal representation among the research teams themselves.

"It's painful again to acknowledge the overt, ugly, dangerous aspects of racism while also, as we all know, acknowledging that the undercurrent of racism has made it very difficult for our brightest and best to even think about going into cancer research [and] health disparities research, but we must continue to try to focus on understanding the science of health disparities and the science of health care delivery," said Judith S. Kaur, MD, Professor of Oncology and Medical Director of the Native American Programs at the Mayo Clinic Cancer Center Florida.

Industry Efforts

An important component of ongoing growth and improvement in the field includes efforts made by industry partners. During the session, representatives from Merck and Roche/Genentech shared their commitment to addressing racial inequity and health disparities.

"First and foremost, we are committed to conducting research to develop novel medicines and vaccines that address important unmet medical needs to help improve the quality and quantity of life for people all over the world," noted Kenneth C. Frazier, Chairman of the Board and CEO, Merck & Co., Inc., who emphasized the importance of clinical research that includes people of varying age, race, ethnicity, and gender.

Building trust and educating the public on the benefits of clinical trials are crucial, Frazier explained. Additionally, he emphasized the importance of increasing opportunities for underrepresented groups to participate in oncology research by removing barriers, such as out-of-pocket costs.

"We have to increase partnerships—and this is extremely important—with minority investigators and those who serve communities of color to help improve the diversity of participants in clinical trials, not just the patients, but the people conducting those trials themselves," he noted.

The industry must also recognize ongoing health disparities. "We're all contending with the COVID-19 pandemic [and] what that has revealed is the stark inequities in our society that have led to a disproportionate impact on people of color," Frazier noted.

Another important component is a diverse workforce within companies like Merck. "If we are not diverse ourselves, there's no way we can serve mankind in its full diversity," Frazier said.

Levi A. Garraway, MD, PhD, Chief Medical Officer, Executive Vice President, and Head of Global Product at Roche/Genentech, emphasized the importance of bringing attention to racial bias. "Calling out that mindset and recognizing [its prevalence] is a big part of countering it," he noted. "And so, we have several ongoing efforts to address these [issues] and certainly one is a large effort in inclusive research.

"In terms of our own culture, [Genentech] recently hired a chief diversity officer who has a team that represents our entire business," he continued. "The fact that we have this in place has allowed us to really center our focus on what progress can look like."

Garraway noted that, while these initiatives are important, you can't just put them in place and expect issues of racial bias to go away. "If you really want to make a sustained change in this area, one needs to be willing to set goals and measure progress towards those goals and have accountability for those goals," he said. "So, there's a lot more that we need to do at Genentech and Roche, but, certainly, we're proud of the steps that we've taken thus far."

Ongoing Commitment

As the session came to an end, panelists urged the cancer community to commit to positive change with a focus on taking action and supporting their colleagues of color as well as holding institutions, companies, and individuals accountable.

"Progress has been made, undoubtedly, but we still have a long way to go," noted John D. Carpten, MD, Professor and Chair of Translational Genomics; Director, Institute of Translational Genomics, University of Southern California Keck School of Medicine. "We have to get to a point where people can begin to feel comfortable recognizing racism, and yes, racism is a hard word.

"We tend to want to use this word diversity and inclusion because it sounds better," he continued. "I think people are more comfortable with that, but we've got to become more uncomfortable if we're really going to move the needle and see racism dispelled in America."

Ribas concluded the discussion with a commitment from AACR. "I'm really grateful for you sharing your thoughts. There's a lot for us to follow up on," he said, emphasizing that now is the time to act. "We're going to follow your leads. We're going to take the challenges and we're going to put our best efforts to change what has happened for so many years. This is not okay; we have to call the things by their name and we're going to do that." OT

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To assess their marker's clinical utility, the researchers analyzed tumor samples from 47 men, pre- and post-surgery, to evaluate its potential to detect cancer recurrence over time. Currently, PSA is used to evaluate biochemical recurrence in the clinic.

As expected, surgery reduced the scores from 55 to 22 about 30 days following surgery; the marker was 96 percent accurate in detecting recurrence. Kidd said such data can provide a baseline to follow patients for any recurrence of disease following surgery.

"We had an opportunity to evaluate PSA in the same cohort," Kidd said. "The (PSA) biomarker was similarly elevated in both BPH and prostate cancer, with an overall accuracy of 50 percent." PSA levels were positive in 86 percent for BPH and 83 percent for prostate cancer, rendering subsequent clinical decision-making based upon PSA levels questionable.

As for next steps, the research team plans to examine whether "omic" analysis and the application of mathematical algorithms to their 27-gene marker can predict specific therapies best suited or effective for individual patients.

The team also expects to conduct a large prospective study to validate the biomarker as a diagnostic with prognostic value. Such data would be of particular clinical relevance for African-American men where aggressive, high-grade prostate disease is prevalent and often diagnosed late.

"We have established two prospective studies in men with an African genetic heritage to assess if the prostate cancer signature in this group can identify disease earlier and facilitate more timely intervention of this disease variant," Kidd said. OT

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