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Bringing Precision to Screening for Cancer

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Precision medicine is most often discussed in the context of treatment, but cancer control and prevention researchers are applying these concepts to cancer screening. Largely, that means finding ways to pinpoint who is most likely to benefit from regular screening.

Cancer control researchers met this fall to discuss the state of the science of precision screening, such as low-dose CT scans for the early detection of lung cancer.
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On September 29, NCI sponsored a conference that brought together leading screening and cancer control researchers to discuss the state of the science of precision screening for five cancers: prostate, breast, colorectal, cervical, and lung.

The intent of the meeting was to allow the researchers "to brainstorm about how best to move forward" with a research agenda for better understanding and implementing precision screening, explained its chief organizer, Pam Marcus, Ph.D., of NCI's Epidemiology and Genomics Research Program.

A surprising theme that emerged from the meeting, Dr. Marcus said, was that although there are some common issues and challenges for precision screening for these five cancers, in many cases, the issues and challenges "are very organ specific."

Harms and Benefits

In recent years the risk of overdiagnosis and overtreatment associated with cancer screening—in particular, screening for breast and prostate cancer—has come under intense scrutiny. The need to reduce those risks was an undercurrent throughout the conference.

"All screening programs can do harm, but some can do good," said Nora Pashayan, M.D., Ph.D., of the University College London, during her keynote address. "What matters is the balance of potential benefits versus potential harms."

Michael Gould, M.D., of Kaiser Permanente Southern California, highlighted the challenges that lung cancer screening can present. Dr. Gould pointed to the changes that have come about as a result of the National Lung Screening Trial (NLST), which showed that current and former heavy smokers were 20 percent less

likely to die from lung cancer if they were screened with low-dose helical CT than if they were screened with standard chest x-rays.

But, he noted, the trial also had a very high percentage of false-positive results, which translated into approximately 2 percent of participants undergoing an invasive procedure—either a biopsy or surgery—for what turned out to be a benign lung nodule.

Based on the NLST results, Medicare and many other insurers now cover the cost of screening with CT in current or prior heavy smokers. But that change has not come without problems, Dr. Gould noted.

As was the case in NLST, he said, many current and former smokers who are now coming in for screening have false-positive results and are undergoing additional tests, including invasive procedures—which can have their own, sometimes serious, complications.

Researchers are studying ways to better stratify these people by their cancer risk, and Dr. Gould described some of this work. But, in the absence of more definitive information on risk beyond smoking history, he acknowledged that, at his institution, "we're still struggling with how to implement screening in the real world."

Progress toward Risk-Tailored Screening

In breast cancer, there has been considerable study of precision screening, also referred to as risk-tailored screening, explained Dr. Pashayan. But, echoing a refrain heard throughout the day, she acknowledged that in this area "there are more questions than answers."

In breast and other cancers, factors such as family history, age, and clinical history are often used to predict future cancer risk, which can help guide screening decisions. Dr. Pashayan and other researchers have been studying whether additional information, such as panels of genetic alterations known as single-nucleotide polymorphisms (SNPs)—identified via genome-wide association studies—can help to improve risk stratification.

She cited a recent large study that indicated that a "polygenic risk score"—based on how many risk variants associated with breast cancer a woman has—can identify women at increased breast cancer risk. In the study, women with the highest polygenic risk score, for example, had a risk of breast cancer that was three times greater than that of women who had lower scores.

Although these results suggest that there is some promise to using this type of genetic information to help identify those who might benefit most from screening, many of these types of studies—in breast but also other cancers—are still preliminary and will need to be refined and validated, Dr. Pashayan noted.

"We will need robust evidence to support precision medicine screening," she said.

Some Movement toward More Precision

Cervical cancer screening in the United States has already moved toward a risk-based approach, said Mark Schiffman, M.D., M.P.H., of NCI's Division of Cancer Epidemiology and Genetics (DCEG).

The shift, he explained, is based on studies which established that persistent infection with high-risk types of human papillomavirus (HPV) are responsible for nearly all cases of cervical cancer and that revealed the

process by which precancerous lesions progress to an invasive cancer.

"We know a great deal about the causal pathway in cervical cancer," Dr. Schiffman said.

Although Pap testing is still being used routinely to screen women for cervical cancer, clinicians are now incorporating a patient's HPV status into the decision-making process, Dr. Schiffman said. Under current recommendations from leading medical societies, the presence of high-risk HPV types, identified using DNA-based tests, should help to guide decisions about issues such as the most appropriate screening interval.

But the current approach is not set in stone, Dr. Schiffman cautioned. As rates of vaccination against HPV increase, he explained, that will affect how cervical cancer screening is performed.

Challenges Remain

There was also robust discussion about what type of evidence is needed to implement changes in screening practices: primarily data from observational, population-based studies or data from randomized controlled trials.

Dependent on the cancer type and the extent and strength of the available data, there is evidence to support both views, Dr. Marcus noted. Working through these sorts of questions will be a key challenge in moving toward a precision medicine-based approach to screening, she added.

Although there is still a long way to go before precision screening is common for these cancers, Dr. Gould stressed that it's important to keep moving in this direction.

"When we're screening, we're dealing with otherwise healthy people, and we're turning them into patients," he said. "We need to do everything we can to [screen people] safely and minimize harms."

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