Bringing evidence to health screening debates

February 19 2017

Gatsonis will speak at the AAAS Annual meeting about how large screening trails are structured to provide the best evidence, not only of accuracy but also for many other pertinent questions regarding patient care. Credit: Peter Goldberg for Brown University

Whether to screen? How often? At what age? At what cost?—seem to readily breed conflicting opinions and public confusion. What's needed

is rigorously produced evidence. That's where Constantine Gatsonis, chair of the Department of Biostatistics at Brown University, comes in.

In a talk and panel discussion at the 2017 annual meeting of the American Association for the Advancement of Science on Sunday, Feb. 19, Gatsonis, a veteran researcher on many large cancer screening studies, will discuss how such trials are designed and conducted to ensure that researchers can evaluate not only the accuracy of a test, but also its cost-effectiveness, its effect on doctor and patient decision-making and its effect on health outcomes.

After all, screening is not just about detection, Gatsonis said, but about health. Patients definitely want their cancers found, but not all accurate, positive diagnoses should lead to treatment.

"There is a growing concern of this notion of over-diagnosis," he said. "Screening is finding small lesions that would not hurt you. Generally speaking with screening, especially as the modalities become more and more accurate and can see smaller and smaller things, the question is, is that good for you? It's not a foregone conclusion."

In his talk, "Evaluating the Impact of Diagnostic Modalities Used in Screening for Disease," and the panel, "Medical Decision-Making: To Screen or Not to Screen?" in Room 309 of Hynes Convention Center at 8 a.m., Gatsonis will outline how large studies and statistical analysis bring data to bear on the many questions that swirl around screenings.

Big questions, big studies

Definitive screening trials feature huge sample sizes to ensure the highest degree of certainty when comparing one method against another. But even when the sample is large and the question is straightforward, the answers won't always be obvious. Gatsonis was the lead statistician

of the Digital Mammographic Imaging Screening Trial, which sought to compare the accuracy of digital vs. film mammograms for detecting breast cancer in a sample of more than 49,000 women. The primary paper from that study was published in the *New England Journal of Medicine* in 2005.

The two technologies turned out to have similar accuracy overall, but with a huge sample and carefully gathered data, the study was able to also show that digital mammography had significantly greater accuracy in women younger than 50 years, women with radiographically dense breasts, and premenopausal or perimenopausal women.

The evidence of some clear advantages gave digital mammography a strong foothold, Gatsonis said: "That study is the study that essentially put digital mammography in every hospital."

Well-structured, thoughtfully designed trials can answer multiple questions. Gatsonis was co-lead statistician for the National Lung Screening Trial, which produced the 2010 finding that among 53,454 current or former heavy smokers aged 55 to 74, those who received low-dose helical CT scans had a 20 percent lower risk of dying from lung cancer than participants who received chest X-rays. The study therefore answered the question of which screening method was better based on health outcomes.

The trial also kept track of costs and so was able to assess that CT screening was cost-effective, at least given certain specific assumptions. The study also gathered the data needed to analyze another pertinent question that isn't always asked: Did false positives—CT scans that inaccurately detected cancer—trouble patients? An analysis led by Gatsonis's Brown colleague Ilana Gareen found that such results did not cause serious concern, at least in part because the study's informed consent procedures were clear about the possibility of the unduly dire-

seeming result.

Gatsonis is now leading the statistical side of a new breast cancer screening study, the Tomosynthesis Mammography Imaging Screening Trial, which will compare the 3D technology of tomosynthesis with standard, 2D digital mammography.

Rather than just assessing accuracy, the trial, which is set to begin recruiting a whopping total of 165,000 U.S. and Canadian women between the ages of 45 and 74, will also focus on a specific clinical outcome that will be readily apparent within four and a half years from their entry into the study. At that point the research team will assess in which group—tomosynthesis or digital mammography—it was more frequent for a woman to be diagnosed with an advanced, aggressive cancer. The data will help to discern the health impact of each kind of screening, without the team having to wait until there was a sufficient number of breast cancer deaths to allow for a comparison based on mortality.

"We're actually trying to bridge the span between accuracy and ultimate outcome," Gatsonis said, and "do so within a reasonably short study."

In addition to using this innovative endpoint for the primary comparison, the trial is promoting a new approach to screening, which incorporates knowledge of breast cancer risk factors and tailors screening to these factors. For example, Gatsonis said, postmenopausal women will be screened annually or biennially depending on their risk profile.

Big screening trials are expensive and logistically complicated. They generate massive amounts of data that must be expertly interpreted to accomplish their goals. But Gatsonis said that's all still better than the alternative of speculative opining.

"Nobody said screening is a simple process," he said.

Provided by Brown University