ONCOLOGY TIMES

Independent News on
HEMATOLOGY / ONCOLOGY

Special Edition Supplement to April 25, 2015 issue

Meeting Reporter:

Miami Breast Cancer Conference

February 26 - March 1, 2015

@OncologyTimes /OncologyTimesNews Wolters Kluwer

'Medical Crossfire Debate'

Is Genetic Susceptibility Panel Testing for Breast Cancer Ready for Prime Time?

BY ROBERT H. CARLSON

MIAMI BEACH—Genetic tests for breast cancer susceptibility that go beyond BRCA1/2 mutations are either a very bad idea or an idea whose time has come, depending on which speaker you listened to in a "Medical Crossfire" debate here at the Miami Breast Cancer Conference.

Not ready, said J. Michael Dixon, MD, Professor of Surgery, Consultant Surgeon, and Clinical Director of the Breakthrough Research Unit, Edinburgh Breast Unit, of Western General Hospital in Edinburgh, U.K., noting that there are limited data on the cancer risk for some of the genes in next-generation sequencing panel tests, and the interpretation of results is difficult. Getting informed consent is extremely problematic, he said, and there are huge issues surrounding variants of unknown significance (VUS).

"Patients at risk of breast cancer should have limited gene testing and not be exposed to the issues and concerns of multiplex gene testing," Dixon said.

The other debater, Pat Whitworth, MD, Director of the Nashville Breast Center, said: "If 'prime time' means access in practices delivering state-of-the-art care throughout the U.S., then panel testing is past 'ready for prime time.'" He said experienced cancer doctors and genetics specialists in leading programs have employed panel testing as a first-line approach for appropriate cases since 2013, and for much longer in certain cases.

J. MICHAEL DIXON, MD: Genetic Testing Not A Prime-Time Player

"So, I'm the curmudgeon," Dixon began, in his typically humorous style, promising to convince the audience that genetic susceptibility panel testing is not ready for prime time.

He began his story with the patenting of BRCA1/2 genes in 1995, by Myriad Genetics. After several rounds in various federal courts, the Supreme Court in 2013 upheld a lower court decision that human genes cannot be patented.

(At this point Dixon showed one of many humorous, and sometimes hilarious, video clips, which a written description cannot possibly do justice to.)

By 2014, there were nine labs offering BRCA1/2 testing, seven offering BRCA1/2 testing as part of a next-generation panel, 14 labs with tests that included BRCA1/2—"and an infinite number of genetic counselors pulling their hair out."

"Just because you can test for these tests doesn't mean you should," Dixon said.

World Health Organization criteria for genetic testing are that:

- The disease has to be an important health problem;
- The risk of the disease in the mutation-carrying disease is high in the general population and not just in the high-risk group;
- The mutations can be accurately identified, to avoid false positives, false negatives, and uncertainties; and
- Effective interventions have to exist.

"The reality is, only BRCA1/2 routinely fulfill those criteria," Dixon said.

Citing examples of what is currently available, he described tests from Ambry

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However, this does carry a small increased risk in local-regional recurrence, he said.

Adjuvant endocrine therapy is likely to be beneficial in reducing local-regional and distant recurrence in older women with hormone-receptor-positive breast cancers who have tumors larger than one centimeter and with estimated survival times exceeding five years, he said.

Triple-Negative Treatment Age Dependent

About 15 percent of elderly breast cancer patients have triple-negative breast cancer—"and it's just as bad in older people as in younger people," Muss said.

Most recurrences are within five years, so estimates of five-year survival are important. "More chemotherapy is better—usually with taxanes and anthracyclines—so estimating life expectancy and toxicity is key," he said. But even patients with a shorter life expectancy can benefit from treatment if the patient has large tumors or many involved nodes.

Anti-HER2 therapy in elderly patients depends on estimated survival, he said. "When there is an estimated survival of more than five years, I treat older patients like younger patients. But if the patient has cardiac comorbidities, order a cardiology consult."

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Genetics, which offers BRCAplus, the GYN-plus, BreastNext, and OvaNext.

"There is a varying number of genes you can get in these populations, but even in their very restricted gene population they've got CDH1—and that's actually a gastric cancer gene. It's rarely related to invasive lobular cancers. Why it's in the breast panel, I'm not sure at all."

One panel also included the STK11 gene, which is not commonly associated with breast cancer, p53, and PTEN, he noted—"These are all pretty rare and usually not presenting with patients with breast problems.

"So the problem with gene panels is that there is limited data on the cancer risk and the penetration for most of these genes in the panels," he said. "And there's no consensus on the management in a lot of these genes when mutations are found."

The National Cancer Institute and the National Institutes of Health maintain that the clinical applicability of these mutations is uncertain, that there is a low mutation prevalence, and that there are weak associations with breast cancer. "And there is a complete lack of guidelines for clinical management—if you find a mutation, you have no idea what to do," Dixon said. "And remember, these are the genes you're planning to test for in those panels."

'Whole Spectrum of Gray'

Furthermore, there is no positive or negative, he said, but rather a whole spectrum of gray. "On one end you didn't get a pathogenic mutation; on the other end, you get a known mutation which is negative. Then at either end you've got variants of unknown significance, which are likely benign or likely pathogenic, and in the middle you've got these variants of unknown significance."

He cited a recent study showing a high prevalence of mutations with VUS in a panel of breast cancer susceptibility genes in BRCA1/2-negative patients with early-onset breast cancer: ***Maxwell KN et al: Nature Genetics in Medicine doi:10.1038/gim.2014.176***.

Another study was a clinical evaluation of a 42 multiple-gene sequencing panel for hereditary care risk assessment: ***Kurian et al: JCO 2014;32:2001-2009***. Among 198 women in that study, 174 had breast cancer but only 57 carried germline BRCA1/2 mutations.

So how do patients cope with these variants of unknown significance? Dixon asked rhetorically. To answer, he cited a study of risk-management strategies for women with VUS for BRCA1/2, versus known deleterious mutations: ***Garcia et al: Genetics in Medicine 2014;16: 896-902***. A total of 69 women had VUS and 305 had BRCA1/2 deletions.

"Thirty percent of those women with variants of unknown significance opted for salpingo-oophorectomy, compared with 74 percent of the patients with deleterious mutations, and 11 percent had their breasts removed," he said.

Eventually it was found that 56 percent of the variants of uncertain or unknown significance could be re-classified as either deleterious or not.

"That took a median of 39 months, but the median time to risk-reducing oophorectomy had been 18 months, and risk-reducing mastectomy had been 20.1 months—the reclassification arrived too late."

Reduce Anxiety?

"Does genetic counseling reduce anxiety?" he asked, and answered citing a study in which 714 women with no family history of breast cancer were BRCA tested, and that was uninformative because they had no mutation (***Culver JO et al: Clinical Genetics 2013;5:464-472***). Seventy one, though, had BRCA VUS.

"There was much less reduction in distress by genetic counseling for women with variants of unknown significance. And only 23 percent of the women with the variants of unknown significance had any reassurance from their counselors—77 percent did not."

The problem with gene panels is that unanticipated mutations are picked up that are not associated with an indication for testing. "And how often are these recommendations correct?" he asked, again citing the Kurian et al study of 198 women, of which 16 had pathogenic variants in a variety of other genes. And the new recommendations in 11 women were: one to have bilateral prophylactic salpingo-oophorectomy; six to have more intensive breast surveillance; and for another six, intensive GI surveillance.

> "Among women who have breast cancer and have a BRCA mutation, only about one third have been identified—we need to improve what we're doing."

"This had nothing to do with their breast cancer—suddenly we're concentrating on the GI system," Dixon said.

NCI guidelines say testing must be focused on identifying the mutation known to be clinically actionable, but many genes in these panels do not fulfill these criteria, he noted, quoting a recent editorial by Susan Domchek, MD, of the University of Pennsylvania (***JCO 2015;33: 295-296***).

"Individuals need to be counseled about any uncertain value of these tests," Dixon said. The real issue, he continued, is that the rapid pace of technological innovation has driven panel testing into the clinic before there is a responsible framework. "Counseling and clinical management

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developed to support single-gene testing just cannot cope with this multiple-gene panel testing."

It must be regulated, he said, adding that the American Society of Clinical Oncology and the American Association for Cancer Research both support this view: "We need laboratory coordination, not competition; and we need clinical and analytic quality to be paramount, because [results from] no one lab will be the same."

Dixon concluded: "Genetic susceptibility panel testing is not ready for prime time, and limited gene testing is all that's required. We need much more information on what are deleterious mutations in genes in these panels and the risk that is associated with these mutations, as well as how to manage women with these mutations. Gene panels cannot be recommended at the present time in evidence-driven health care systems."

PAT WHITWORTH, MD: Panel Testing is Ready, so Doctors Need to be Too

Whitworth began with a quote: "Don't let the fear of the unknown keep you from changing what you know doesn't work." Panel testing works, and it's ready right now, and doctors need to be ready, he said.

Whitworth, who identifies himself as a strong advocate for panel testing, said: "Panel testing is ready for prime time, it is prime time, it's here, and there's no putting the genie back in the bottle. Doctors aren't ready, but they need to be. And doctors need education, because you can't make mistakes with this kind of technology."

Whitworth said physicians need to use the technology on behalf of patients who need it: "We are not doing a good job right now—in fact we're doing a terrible job with BRCA testing. We are not testing people who need to be tested, we're not delivering the care that needs to be delivered, and that's because the system we're using is inadequate."

Presently, in the U.S. there are 220,000 unaffected carriers for just the pathogenic BRCA mutations, but only six percent have been identified, he said. "Yes, we need to be concerned about over-testing and inappropriate testing; we need to be educated, we need to do testing right. But we are not getting this job done."

> "Counseling and clinical management developed to support single-gene testing just cannot cope with this multiple-gene panel testing."

Whitworth said that among women who have breast cancer and have a BRCA mutation, only about one third have been identified—"we're doing a bad job, and we need to improve what we're doing."

He quoted Mary-Claire King, PhD, who identified the BRCA1/2 genes: "If we identify carriers only after they develop cancer, that's a huge failure."

Two Concurrent Challenges

Two challenges are happening at exactly the same time, Whitworth continued: "First, we're not delivering the care we need to deliver with BRCA testing. Second, that could have a dramatically expanded capability to test other genes linked to breast cancer risk at the same price, or probably less."

The only solution is physician education, Whitworth said. "If you think you're just going to refer the patient to the genetics counselor and the problem's going to be solved, you've got another thing coming. Physicians involved need to be very educated. The counselors are going to be a key resource, they're going to be collaborators, but they cannot possibly handle what's coming."

Panel testing is now standard at many institutions, and selected populations are going to be tested in a population based load, for highly penetrant genes. "In 10 or 20 years, whole genome sequencing or whole exome sequencing is probably going to guide management—not just in cancer, but in cardiology and in pediatrics, and there are ways to get there safely."

Whitworth addressed Dixon's objections, and agreed with the first, that knowledge is incomplete: "We don't know as much as we will in the future, but we already know what to do with these results. What we are lacking are guidelines. But guidelines are not for leaders, they're for followers."

'Patient Stress Will Decline, Not Increase'

The criticism that patient stress will increase with panel testing and that mastectomies will increase are not true, Whitworth maintained. "Both of these will go down if we do a good job of educating doctors."

Doctors will have to make recommendations based on limited information, "but that's what we do every day. And we will make mistakes, but that's no reason to stop the whole program."

Whitworth pointed out that the third leading cause of death in the U.S. is mistakes—"but we haven't closed all the hospitals yet."

'Most Exciting Thing…'

The most exciting thing about panel testing is that when a patient in a family with a known pathogenic mutation has a negative test, she no longer has the high risk she's terrified about. "She has ordinary population-level risk and she can be screened as the ordinary population is screened," Whitworth said. "This can decrease wasted resources and patient distress by half.

"And it's not just her—it's the other women in her family who are also terrified, who also get off the hook once they have a negative test for this

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mutation that's been identified in the family."

By going from high-risk screening to ordinary screening, he said, "we stop doing a biopsy for every little thing that goes bump in the night on the mammogram, and we have fewer fear-based mastectomies.

"Believe me, women are having fear-based mastectomies just based on the family history," he said.

But even a positive test in the family directs resources appropriately. That patient can get, and needs, and will benefit from, high-risk screening, maybe chemoprevention as well, he said. And certainly she'll get a bilateral salpingo-oophorectomy, if this is a BRCA mutation.

"And there we are targeting resources, not mastectomies."

Whitworth showed many video clips of his own—at this point a clip of President Roosevelt saying, "The only thing we have to fear is fear itself."

Whitworth listed some of the genes Dixon had discussed, saying: "These are not stomach cancer genes, or breast cancer genes, or ovarian cancer genes; these are DNA repair genes for the most part. Almost all of these in these panels, with a few exceptions, are DNA repair genes.

"Remember that the healthy person has about 10 billion single nucleotide polymorphisms, and the vast majority of mutations are benign."

A massive increase in VUS will not lead to widespread chaos or unnecessary mutilating operations, he said. Rather, it will be a major public benefit—if combined with well-designed research and managed appropriately by educated clinicians.

'Keep Clinical Point of View'

Whitworth said the way to manage VUS is by keeping a clinical point of view. "When I started doing BRCA testing in the late 1990s and early 2000s, I made this mistake: I was very fascinated by these variants, and instead of a clinical point of view, I took a scientific point of view, thinking that 'this is fascinating, maybe we'll find something out.' That's exactly the wrong point of view.

"In pre-test counseling with the patient, and certainly in post-test counseling, the patient needs to understand that a VUS does not explain her family history. And it means literally nothing, absolutely nothing for patient care."

Whitworth said action based on a VUS finding is not appropriate at any time—"and the care of the patient is for family history, just like we always do.

'Take No Action Based on a VUS'

"No action should be taken based on a VUS, not ever," he stressed.

Further knowledge about BRCA will come from broad commercial availability, and from following up on every VUS and doing genetic analyses in the family. "This can't happen any other way," Whitworth said. "If we tried to fund it by gigantic, randomized trials to do the same thing, it would be year 3000 before we got it done."

In the meanwhile the VUS rate will rapidly go down once this information becomes available, he said. "In fact, since 2002, the VUS rate in African-Americans has gone down from about 40 percent to below five percent. The only way this happens is with broad commercial availability."

Whitworth summarized his remarks by reiterating that it is already prime time for panel testing, and it should be best practice, because:

- The cost is about the same as single-gene test;
- The cost and distress are far less than with sequential tests;
- Panel tests are 50 percent more likely to explain strong family history;
- Positive tests cut waste and distress by half; and
- Educated physicians know how to provide pretest counseling, how to team up with genetic counselors, and how to keep a clinical view when managing a VUS finding.