A new blood test designed to close the gap left by mammography may be on the horizon and, if so, the women of Oklahoma will have made a unique contribution.

On September 23, 2009, Dr. Alan Hollingsworth, Medical Director of Mercy Women's Center, attended a meeting in Berlin, Germany of the Scientific Advisory Board of DiaGenic ASA, a biotechnology company that timed their annual meeting to coincide with the 15th Congress of the European CanCer Organization (ECCO-15). Results of a research study were presented at ECCO-15 by DiaGenic ASA, based in Norway with Mercy participation, showing for the first time that breast cancer can be detected from blood samples in women with a type of breast cancer that is often invisible on mammography. Over 1,500 women contributed to the overall study, while the Berlin presentation focused on those women with the lobular type of breast cancer that tends to evade early detection. Mercy Health Center was the only participating site in the United States for the study, while the remaining 5 sites were from various European countries.

Dr. Hollingsworth is one of four physician-scientists who serve on the breast cancer division of the Scientific Advisory Board of DiaGenic. Dr. Hollingsworth is the only representative from the United States, while other board members include: Dr. Martine Piccart, one of the most prominent breast oncologists in the world, immediate past-president of the European Organization for Research and Treatment of Cancer (EORTC), and founder of the Breast International Group, which is a consortium of 38 breast cancer research groups; Professor Anne-Lise Borresen Dale, Head of the Department of Genetics at the Norwegian Radium Hospital in Oslo and current president of the European Association of Cancer Research; Dr. Christos Sotiriou, Head of the Functional Genomics and Translational Research Unit at the Jules Bordet Institute in the Universite Libre de Bruxelles, Belgium.

Hollingsworth has been drawn to the concept of a blood test to detect breast cancer for the past 16 years, starting with an article published by a scientist in Israel who indicated it might be possible to detect breast cancer from a blood sample. "At the time, I was discovering that mammograms missed more cancers than people were being led to believe," said Hollingsworth, "and too, I was seeing the hope of breast MRI in its developmental stages. Back then, I knew MRI was going to be revolutionary, but at the same time, totally impractical for asymptomatic screening in the general population. We would need a blood test to tell us when to order an MRI in the face of a normal mammogram."

"I had organized a weekly breast cancer research meeting at the university, and it was one member of that group, Dr. Paul McKay from the Oklahoma Medical Research Foundation, who had come across the first article ever published, to my knowledge, on a possible blood test to detect early breast cancer," said Hollingsworth. With the backing of a number of community leaders, including the late Patricia Browne and the original board members of the OU Breast Institute, Dr. Hollingsworth and OMRF arranged for the scientist from Israel to travel to Oklahoma City to discuss formal clinical trials on her proposed blood test.

"Although that original pursuit dead-ended, it started my personal quest to help develop a screening blood test to capture the cancers missed by mammography," said Hollingsworth. "After I moved to Mercy Health Center, the administration supported my vision, and since 1999, my staff & I have managed to distribute over 7,000 blood samples to eight different research groups in academics and industry. Most researchers have hit the same dead end we did with our scientist from Israel, but the group from DiaGenic has a unique approach, and one that I'm going to concentrate on. Rather than the usual strategy of trying to find a key protein in the blood, like PSA for prostate cancer, the Norway group has focused on circulating white cells, which change their genetic expression profile in response to breast cancer.

"Pathologists have noted for many years that lymphocytes and other immune cells will surround milk ducts that are filled with breast cancer cells, even at the 'in situ' stage, called DCIS, very early in the process before there's any threat to life. In other words, the body knows something is wrong, long before the cancer becomes a threat. It turns out that those lymphocytes re-enter the circulation, or cross-talk to the circulating lymphocytes, such that we can identify alterations in genetic expression in those white cells by analyzing their RNA, the first product of DNA. RNA is very difficult to work with, requiring special collection tubes plus storage and shipping problems, such that after my initial conversations with the Norway researchers, we decided it would be too difficult for us to offer help from the United States. That's why the development of this test has been based in those countries in close proximity to Norway. Yet, the need for some U.S. samples became so great, DiaGenic re-opened the dialogue a few years later and visited Oklahoma City to inspect my protocols. After that visit, the collaboration began, and I was subsequently asked to join their Scientific Advisory Board."

For the past 10 years, at Mercy Women's Center, Dr. Hollingsworth's research project has asked women who are undergoing breast MRI, or who are having a biopsy performed, to donate a blood sample under an approved protocol. The unique feature of this research repository of blood is that each sample is accompanied by an extensive database plus breast MRI results. "It is the MRI component that makes our blood samples unique in the world, in what's called an 'annotated specimen library'. If you're trying to develop a blood test that finds cancers missed by mammography, it's going to be hard to do if you've only performed a mammogram. Without MRI, you really don't know what's going on in the patient's breast tissue, so a sample labeled "benign control" could actually be from a patient with cancer. Once word got into the research community about our specimen bank being linked to MRI outcomes, I no longer had to search out collaborators."

Surprisingly, the development of a screening blood test for breast cancer has been a low priority in the research community. The first National Cancer Institute grant was not awarded until 2004, whereupon Dr. Hollingsworth contributed blood samples to the Fred Hutchinson Cancer Center in Seattle, the recipient of the grant. Only a handful of research groups have been devoted to this cause over the years. "The lack of interest has been due to a mistaken belief about mammography," says

Hollingsworth. "The sensitivity for mammography to detect cancer has been oversold to the public as being 90%. In fact, in head-to-head comparisons of MRI to mammography, when all 7 studies are tallied, the detection rate of mammograms alone is only 40%. Surprisingly, it takes *both* mammography *and* MRI to exceed 90% detection."

BCTect™ is the result of this vision, and the blood test will be released by DiaGenic ASA in 8 European countries: Austria, Denmark, Finland, Greece, Norway, Sweden, Switzerland, and Turkey. A different version of the test will be released in India. "Like most medical diagnostics, the test isn't perfect, but it seems to work for all stages of breast cancer, including the earliest form of DCIS, and the accuracy extends across all the different types of breast cancer as well. While several groups have published their blood test results in the medical literature, our work represents the first time anyone has detected cancer in the face of those tumors that are notoriously difficult to detect by mammography. And, of course, the blood test will continue to improve. Soon, we'll be looking to see if the newly described microRNA molecules might be helpful."

Is this a breakthrough? "Well, a first step in the right direction is more accurate," says Hollingsworth. "Science is really about many small steps, the vast majority of which end up nowhere. Yet, there is a tendency to announce all the small steps as breakthroughs. In this case, whether it's our blood test or someone else's, this is an important first step. Fifty years from now, screening the general public for cancer using expensive imaging techniques will be a thing of the past. Cancer screening will be accomplished through blood or urine samples, or techniques not yet imagined, and the expensive imaging will be done as the second step in order to localize the tumor and for biopsy confirmation. In fact, cancer visionaries have already started work on incorporating therapy with diagnosis. Thus, the scenario could easily be a screening blood test and, when positive, an imaging technique that both identifies the tumor *and* allows it to be eradicated with targeted therapy at the same time."

More clinical trials to validate the BCtect™ blood test will be required before the test is available in the United States, and Mercy Women's Center will be making the announcement when the time comes. "This is not a stand-alone test," says Hollingsworth. "It is designed as a prompt for physicians to order additional imaging when mammograms are negative, or to help radiologists decide whether or not a biopsy is needed for an equivocal finding on breast imaging. Currently, the decision to order an MRI for asymptomatic screening is based on lifetime risk levels, which is an inefficient approach, not to mention the fact that this approach excludes the vast majority of women who are going to develop breast cancer. The best way to use MRI is to have a blood test that tells you there's a high chance of cancer at the time of the proposed MRI, *not* the probability of cancer 20 years from now, as is the current standard using lifetime risks.

Whether or not BCTect™ becomes a standard of care or another research group emerges with a better test, it is assured that the women of Oklahoma have contributed

in a most unique way to this dawning of a new era in breast cancer diagnosis – and, that collaboration in top-notch medical research can still come from community hospitals. Dr. Hollingsworth notes, “My profound thanks are offered to Mercy and the women of Oklahoma who facilitated the research, not only those who donated samples but also to the community leaders who offered the original support, all believing that we could do great things in Oklahoma.”