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Marshfield Clinic
Research Foundation

Personalized Medicine
Research Project

Company successfully tests new cardiac risk assessment tool with help from the PMRP

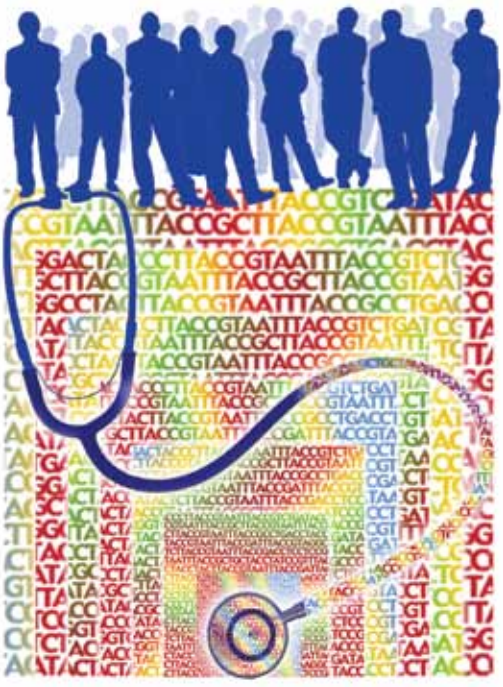
Imagine a single blood draw that provides a more accurate five-year risk assessment for a cardiac event than the current standard.

The first PMRP collaboration with industry is seeking to verify just such a test using PMRP blood samples. Details of the collaboration were presented in January to a meeting of the PMRP Community Advisory Group.

The current way doctors determine your risk of a heart attack is the Framingham Risk Score, which considers age, gender, blood pressure, total cholesterol, HDL (good) cholesterol, smoking and diabetes. The Framingham algorithm calculates 10-year risk of death by heart attack and coronary event. You can find the calculator online at http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof. Unfortunately, clinical cardiac evaluation misses many of the people who are at risk. Sixty-two percent of cardiac events happen to people with 0 or 1 risk factors.

The new test has the potential to solve this problem. It measures a number of biomarkers (proteins) circulating in the blood – biomarkers that are associated with the biological processes of atherosclerosis and unstable plaque formation. The test combines these biomarkers with traditional risk factors, including age and blood pressure, to develop an algorithm, or predictive tool, that can calculate an individual's risk of a cardiac event within five years.

But before a test can be accepted as valid, its developers have to demonstrate that the algorithm could be used in different



populations and "verified." This is where the PMRP comes in. The collaboration began in 2008 when PMRP was contacted for exploratory discussions.

"PMRP was such a great resource because we have blood samples that were drawn when participants enrolled in the study," said Deanna Cross, Ph.D., project scientist. "Many of these people continue to get care within Marshfield Clinic, so we can follow their health for five or more years."

Finding biomarkers in one population has been done for a number of different populations. What has been lacking is

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Inside

DNA DAY

A special day for DNA

National DNA Day (April 15) is a unique day when students, teachers and the public can learn more about genetics and genomics! The day commemorates the completion of the Human Genome Project in April 2003, and the discovery of DNA's double helix. Check out the redesigned National Human Genome Research Institute (NHGRI) Web site (http://www.genome.gov/dnaday/) for news about this and all the institute's research programs, educational resources and career opportunities.

From the Director

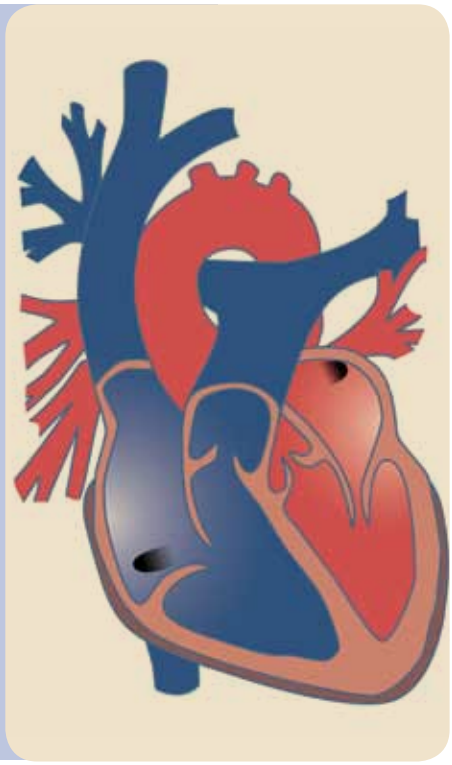

Cathy McCarty, Ph.D.

We received a letter through the PMRP Web site asking how our research is making a difference in patient care, and where all the research dollars go. I wrote back and want to share my responses in the newsletter because they were good questions, and many of you probably are wondering the same things.

I'll start with "Where does the money go?" At the advice of the Community Advisory Group (member names listed in the back page of the newsletter), we had a story in our May 2010 newsletter (available on the PMRP Web site at http://www.marshfieldclinic.org/proxy/MCRF-Centers-CHG-Core-Units-PMRP-Newsletter-May-2010.1.pdf). This article outlined the steps in the research process. Even a small study usually takes at least two years from start to finish and time truly is money. The lab component has decreased in price as technology improves, but still remains very costly. For example, we have conducted a genome-wide association study (GWAS) as part of the eMERGE network. GWAS provides more than 600,000 genetic markers per person and allows us to conduct very sophisticated analyses to discover the genetic basis of disease. These GWAS laboratory tests cost $450 person and because of the number of markers, we need at least 3,000 subjects for these studies. That adds up to a lot of money! Ultimately, we would like to analyze all 3 billion base pairs that make up a person's genome for all 20,000 PMRP participants. Currently the cost is several thousand dollars per person but these costs are decreasing rapidly. The cost to store and manage all that information is high too.

And now for the question of how soon our results will impact clinical care. Let's look at this from the standpoint of an individual. As you might recall, participants in PMRP signed a written informed consent document prior to enrolling in the study. One of the points in this document is that genetic results will not be shared with participants. When PMRP was started in 2002, this made sense because we were measuring only a handful of genetic markers in a research setting and all research results need to be replicated. As technology improves and we have more genetic information, and as more discoveries are made, the results potentially have what we call "clinical relevance." We had an initial discussion with the PMRP Community Advisory Group in January about the logistics of potentially returning research results to study participants in the future if they wanted them. We know not everyone would want to have this information, but as scientists we want to make a difference. From a population standpoint, the article in this newsletter about the project with industry describes a potential practical application of our study results. Ultimately, third-party payors (e.g., insurance companies) will have to be convinced about our study results to cover genetic testing.

As you will see from one of the articles in this newsletter, we are currently enrolling men into PMRP who have had prostate cancer. If you or someone you know is interested in participating please call us at 715-389-7733, or toll free 888-334-2232, press 1. As always, I personally thank each and everyone who has participated! And thank you to the study participant who took the time to write in. Keep those comments coming!



Company successfully tests new cardiac risk assessment tool with help from the PMRP *(continued from page 1)*

the ability to use these same biomarkers to predict many different populations. But this time it worked, in the PMRP and three other biobanks across the country.

The PMRP collaboration employed a case-cohort design using individuals between the ages of 40 to 80. "Cases" experienced an initial non-fatal heart attack (n = 164), or unstable angina (n = 217), up to five years after enrollment. "Controls" (n = 1,058) were selected from the general PMRP population.

The results: the biomarker panel predicted heart attack and unstable angina just as well as the Framingham model, and may better identify individuals within the Framingham's clinically broad "intermediate risk" category who will go on to have a heart attack within five years. Sixty percent of the group considered intermediate risk are undertreated. When the test becomes available, patients that are reclassified as high risk may be treated more aggressively.

"One of the difficulties of the current system is that most people end up in the 'intermediate risk' category," Dr. Cross said. "Unfortunately, there are no clear guidelines regarding whether and how to treat people in this category. While the new biomarker test does not move everyone out of this category, people at high risk in the next five years are more likely to be identified for treatments such as lifestyle modification or cholesterol lowering medications."

Lynch syndrome: genetic counseling can save lives

It is common knowledge that breast and ovarian cancer can run in some families. But, do you know that an inherited form of colon cancer is actually more common?

One in 35 patients with colon cancer has a condition known as Lynch syndrome. In the general population, this means that 1 in 500 people have Lynch syndrome, otherwise known as Hereditary Nonpolyposis Colorectal Cancer (HNPCC). Lynch syndrome predisposes a person to a lifetime 80 percent chance of getting colon cancer in their lifetime, and if they are female, up to a 70 percent chance of getting endometrial (uterine cancer). It increases the risk for developing other rare cancers as well.

With screening and awareness it would be possible to prevent or detect the cancer early if people with the condition and their doctors knew they were at risk. This is why the genetics team at Marshfield Clinic has developed a tool to help providers look for clues that a family could have Lynch syndrome.

In general, genetic counseling is recommended for anyone with the following personal or family history:

- Colorectal cancer before age 50
- Uterine cancer before age 50
- 2 or more Lynch syndrome cancers** in the same person, regardless of age
- A family history of Lynch syndrome

***colorectal, uterine, ovarian, stomach or small bowel, pancreas or biliary tract, ureter/renal pelvis, brain, sebaceous adenomas*

If you have concerns about your personal or family history, talk to your provider about Lynch syndrome and whether or not you might be referred for genetic counseling. In some cases, there are tests that can be done on tumors to see if there are clues that the cancer was caused by Lynch syndrome; in other cases, genetic testing is medically appropriate. Most insurance companies, including Medicare, often pay for genetic counseling and testing when medically indicated. Laws exist to protect us from genetic health insurance discrimination.

Lynch syndrome ties into a study underway in Marshfield, led by PMRP co-investigator Deanna Cross, Ph.D. It is a comparative effectiveness study regarding the use of KRAS screening and Lynch syndrome testing, two genetic tests used in colon cancer screening and treatment. The focus of the Lynch syndrome portion of the study is to determine what system doctors currently use to order a test for Lynch syndrome, and to see if new rules suggesting more people get screened for Lynch syndrome have increased orders for the test. Dr. Cross will be the lead author on the publication of results.

The study is being done across the HMO Cancer Research Network, of which Marshfield is a participating site. The network consists of the research programs, enrolled populations, and data systems of 14 health maintenance organizations nationwide, and is funded by the National Cancer Institute.

Lynch syndrome is named after the man who first described the condition in 1966, Henry Lynch, M.D., of the Creighton University School of Medicine. To learn more, go to http://ghr.nlm.nih.gov/condition/lynch-syndrome.

To contact the Marshfield Clinic Medical Genetics Department, call 877-216-8535 and ask to talk with a genetic counselor.

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Spring event canceled

A reception and short program providing an update on PMRP research, announced for April 25, 2011, has been canceled due to scheduling conflicts. The PMRP researchers and staff apologize, and will try to schedule a similar event in the future.

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Recruits needed for prostate study

Recruitment of 400 men has begun for a study of genetic markers relevant to prostate cancer. Deanna Cross, Ph.D., will investigate genetic markers as a way to make better predictions on secondary complications of radiation therapy for prostate cancer patients.

The study is open to men at least 18 years of age who live in Wisconsin and receive healthcare from Marshfield Clinic. The study seeks patients who have been diagnosed with prostate cancer – and who have undergone radiation therapy but have not had a prostatectomy. Recruits do not have to be current participants in the PMRP, but will be enrolled as part of the study.

The study will use the electronic medical record to see if certain other diseases like diabetes or behaviors like smoking - or the type of radiation treatments - are also important for determining who will react poorly to radiation treatment.

"The hope is that one day we can use both genetics and clinical facts to predict if a man will do badly with radiation, so that we can do something different," Dr. Cross said. "This is what the idea of personalized medicine is all about, tailoring the treatment to the individual by using all the information we know."

The study is supported by KL2 Scholars Program funding from the University of Wisconsin Institute for Clinical and Translational Research (ICTR). Dr. Cross is the first Marshfield Clinic researcher to be named a KL2 Scholar.

The study is the first in the PMRP to use interactive kiosks to enroll participants. The PMRP is believed to be the only biobank using computer-based enrollment. Video and text is used to present enrollment information necessary for informed consent.

Approximately 1 in 6 men will be diagnosed with prostate cancer, according to the National Cancer Institute. In 2010, an estimated 218,000 new cases were diagnosed in the United States, and 32,000 men died. From 2003-2007, the median age at diagnosis was 67, and the median age at death was 80.

If you are interested in participating, an appointment will be scheduled for you. You will receive $20 for your participation, and an additional $10 for completing a dietary history questionnaire. Contact us at 715-389-7733, or toll free 888-334-2232, press 1.

Contact Us

This newsletter is a publication of the Personalized Medicine Research Project, Marshfield Clinic Research Foundation, 1000 N. Oak Ave., Marshfield, WI 54449-5790.

To contact the PMRP, phone 1-888-334-2232, press 1 or 715-389-7733, or visit the PMRP on the Web at http://www.marshfieldclinic.org/chg/

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