Personalized Medicine

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The "Fore a Cure" golf event, held Aug. 27, 2007, at Greenwood Hills Country Club in Wausau, benefited breast cancer prevention efforts at Marshfield Clinic. One of the Clinic teams (from left): Rezwan Islam, M.D., Pat Kinney, Rick Schurman and Gary Zimbric, M.D.

Inside

Study examines breast cancer drug effectiveness

Tamoxifen has been used for the treatment of estrogen receptor (ER) positive breast cancer since the 1970s, and is currently the most commonly used endocrine treatment for breast cancer worldwide.

But despite its proven efficacy in breast cancer treatment, clinical response to tamoxifen is highly variable.

Adedayo Onitilo, M.D., an oncologist-hematologist at Marshfield Clinic-Weston Center, has begun a validation study — utilizing the Personalized Medicine Research Project (PMRP) — to examine whether specific genetic polymorphisms influence clinical response to tamoxifen. (A polymorphism is a common variation in the sequence of DNA among individuals.)

Adedayo Onitilo, M.D.

Dr. Onitilo is assistant director of Clinic Research-Eastern Division.

While the genetics of breast cancer risk have been explored relative to these candidate genes, examination of how these

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Personalized Medicine Research Project: the first five years

The Personalized Medicine Research Project (PMRP), launched in 2002, was a logical outgrowth of initial genomic research. If doctors can understand which genes and environmental factors are involved in a disease, they may be better able to target the disease with specific medications. This information might also enable doctors to predict the risk of disease in an individual and prescribe preventive measures.

"Given the resources of Marshfield Clinic, the concept of the Personalized Medicine Research Project was a fairly simple one," said project founding director Michael Caldwell, M.D., Ph.D. "Collect as many of the people in the Marshfield Epidemiologic Study Area (MESA) as we could who would permit us to have access to their electronic medical record, and they would then give us samples of DNA, serum, and plasma, so that we could perform studies in pharmacogenetics, genetic epidemiology, and population genetics."

In its first five years, the PMRP has become the largest population-based genetic research project in the United States, involving more than 19,000 MESA residents.

Projects that have utilized the personalized medicine database include Marshfield's development of a warfarin dosing calculator and discovery of a new genetic association with warfarin. Warfarin is a frequently prescribed drug used to thin the blood and prevent blood clots, but severe (sometimes fatal) bleeding can occur when patients receive more than their personalized amount of drug. It is anticipated that a soon-to-be-launched clinical trial – the only prospective clinical trial for warfarin funded by the federal government – will result in the calculator becoming the standard of care for warfarin patients across the nation. The Marshfield warfarin study group, led by Dr. Caldwell, developed the dosing calculator based on genetics, age, body surface area and medical procedure. Funding for the trial will come from the Agency for Healthcare Research and Quality.

CURRENT PMRP PROJECTS

Pharmacogenomics and Risk of Cardiovascular Disease (PARC): This landmark study is designed to show how genetic differences can influence a person's response to the type of cholesterol-lowering drugs known as "statins." The $14 million multi-center, five-year study is funded by the National Institutes of Health. Marshfield Clinic Research Foundation has received nearly $1 million for its part of the project. (Led by Russell Wilke, M.D., Ph.D., and Cathy McCarty, Ph.D.)

Hypertensive heart disease: Marshfield researchers are studying the relative importance of genetic variation associated with certain neurohormonal regulatory elements on remodeling (changes in form or function of the heart after injury to the left ventricle) during hypertensive heart disease. (Led by Nader Ghebranious, Ph.D., and Cathy McCarty, Ph.D.)

Osteoporosis: A study is underway to learn how specific genetic factors involved in bone development may be associated with osteoporosis, and to understand the interplay between these genetic factors and environmental factors such as cigarette smoking and use of cholesterol-lowering medications such as statins. (Led by Philip Giampietro, M.D., Ph.D.)

Fibromyalgia syndrome: The aim of the study is to determine if the APOE4 geneotype status is correlated with the diagnosis of fibromyalgia syndrome (FMS). To date, the diagnosis rests solely on physical examination findings and historical features. (Led by Jonathan Reeser, M.D., Ph.D.)

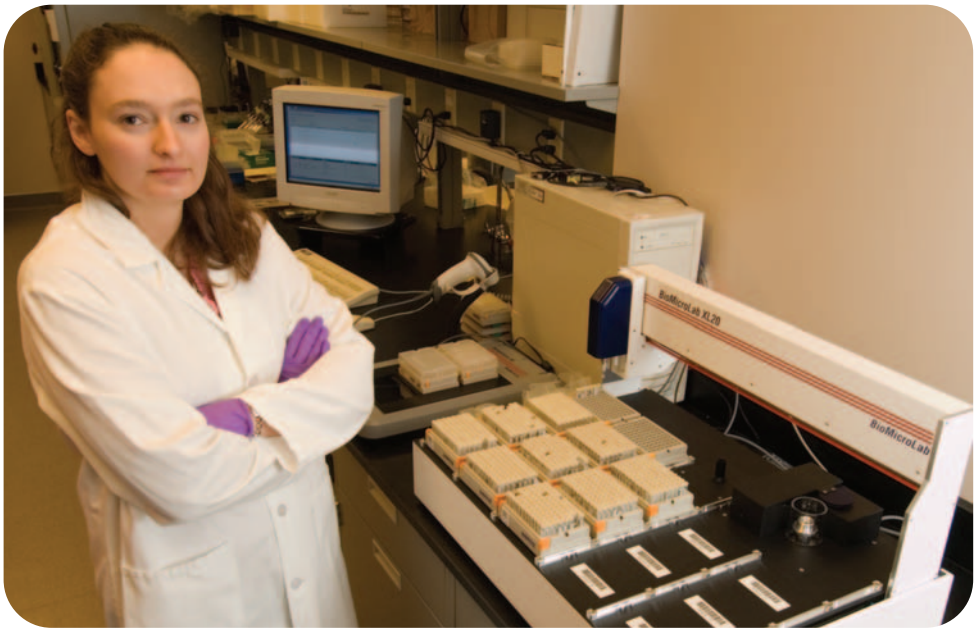
Breast cancer pharmacogenetics: The goal of this study is to examine whether specific genetic polymorphisms influence clinical response to the drug tamoxifen. While the genetics of breast cancer risk have been explored relative to these candidate genes, examination of how these genetic polymorphisms relate to tamoxifen therapy and treatment outcomes as proposed in this study is novel. (Led by Adedayo Onitilo, M.D.).

Multiple sclerosis (MS): The broad objective of the study is to identify the genetic variants that contribute to the pathogenesis of MS in patients from rural Wisconsin. (Led by Khemissa Bejaoui, Ph.D.)

Vertebral malformations: The purpose of this study is to determine if genetic alterations or mutations in three particular genes can be identified in previously banked study subjects with congenital vertebral malformations and available parental DNA samples; and to expand the existing cohort of individuals with vertebral malformations by enrollment and collection of additional patient DNA and appropriate parental and sibling DNA samples. (Led by Philip Giampietro, M.D., Ph.D.)

Cholesterol / obesity: A study is underway to evaluate five genetic markers to see if they predict who does or does not develop bad lipid values in people who have a body mass index of 40 or greater. (Led by Cathy McCarty, Ph.D., and Russell Wilke, M.D., Ph.D.)

Cataracts and low-HDL: (Led by Cathy McCarty, Ph.D.) Story on next page.



Sherri Reisner, Research Associate for the Personalized Medicine Research Project, with the new, automated tube handler.

From the Director

Cathy McCarty, Ph.D.

Welcome to the fourth Personalized Medicine Research Project (PMRP) newsletter. Please note on the back page that we have two new additions to the PMRP Community Advisory Group. I am delighted to welcome Colleen Kelly and Phil Boehning.

I want to thank Robin Yonker whom many people met when they enrolled in PMRP. She served with commitment and enthusiasm in the role of Research Coordinator for five years. She recently moved to Arizona and will be missed. We welcome Yvonne Cerne into the position of Administrative Secretary, taking over from Marion Naugle who served in that role with her sunny disposition until August 2007.

In addition to the federal grants that we have received (discussed below), PMRP is recognized through invitations to speak at various meetings. In June, I presented an overview of PMRP at the Institute of Medicine in Washington, D.C., and Dr. Francis Collins, the Director of the National Human Genome Research Institute, was speaking about the future of genomic research. I was honored to speak to a community group at Mayo Clinic in September as they begin discussion and plans for a biobank similar to PMRP. We hope to develop collaborations on research projects with scientists at Mayo.

As I look back the first five years since enrollment started, I am proud of where we have come as the largest population-based biobank in the U.S., and all of the completed, active and planned projects resulting from PMRP. In the next newsletter, we will have more research study results to share with you. These studies would not be possible without the participation of many, many people, including scientists, clinicians and research participants. As of September 1, 2007, 19,689 people had enrolled in PMRP. I thank you all and congratulate you on your choice to help us advance medical research through study participation. Enrollment is still open, so if you know anyone who is 18 years or older and lives in one of the 19 Zip codes around Marshfield, please tell them to stop by the Lawton Center on the Marshfield campus or to call our toll free number, 1-888-334-2232 or 715-389-7733.

Late breaking news! Large grants help tap PMRP data

Two recent grants will help researchers probe deeper into the PMRP database for answers to some of mankind's most pressing disease problems. See future newsletters for further details as these studies develop.

– The National Institutes of Health has awarded the PMRP $3.2 million for four years to develop and validate electronic phenotyping algorithms to identify cases of cataract and low-HDL (good cholesterol) in the PMRP, and to quantify the impact of two environmental factors (cigarette smoking and statin use) on those diseases.

Cataract and low-HDL are two specific yet interrelated diseases. By examining them in this whole-genome association study – and incorporating environmental risk factors – researchers hope to glean novel data about the causes of the two separate diseases, as well as interaction between them.

The PMRP's portion of this five-center study is built upon the world-renowned strength of Marshfield Clinic's electronic medical record. If cataract and low-HDL cases and controls can be identified electronically, it would eliminate the need for in-person return visits by study participants.

– The National Institutes of Health (NIH) has awarded the University of Wisconsin's new Institute for Clinical and Translational Research $41 million over the next five years. As a partner of the Institute, Marshfield Clinic stands to receive several million dollars to further develop tools, such as the biomedical informatics program, to better study chronic diseases and other conditions.

"This is very good for Personalized Medicine," said Cathy McCarty, Ph.D., director of the PMRP. "ICTR and the grant award are about infrastructure and decreasing time from scientific discoveries to improving health care. Under this umbrella, we're hoping we'll have more regular conversations and engage researchers from the UW to use the resource in collaboration with us. And once we've made discoveries, we want to design clinical trials through an efficient infrastructure from design phase to the clinical setting."

Dr. McCarty will help teach UW scientists about Personalized Medicine and the DNA biobank available for their research.

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Study examines breast cancer drug effectiveness

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genetic polymorphisms relate to tamoxifen therapy and treatment outcomes, as proposed by Dr. Onitilo and his co-investigators, is novel.

The title of the project is: "A Pilot Study on the Association Between Polymorphisms in Estrogen Receptor Genes and Clinical Outcomes in Breast Cancer Patients Receiving Tamoxifen Treatment." The primary goal of the study is to examine whether specific genetic polymorphisms influence clinical response to tamoxifen.

There are about 500 women in the PMRP with breast cancer. The study will be conducted with about 250 women who have been treated with tamoxifen.

In breast tissue, tamoxifen interferes with estrogen binding and essentially deprives estrogen-dependent tumor cells. Estrogens are well established as playing an important role in the potency of breast cancer.

Tamoxifen has proven effective against all stages of breast cancer in premenopausal and postmenopausal women, and is presently the only agent approved by the Food and Drug Administration (FDA) for breast cancer prevention.

Co-investigators in the study are nationally-renowned David Flockhart, M.D., Ph.D., Indiana University School of Medicine, and Jin Yan, M.D., Indiana University Cancer Center. The relationship with Dr. Onitilo was forged through the Pharmacogenetics Research Network (PGRN). The mission of the PGRN is to advance knowledge of the genetic basis for variable drug responses, which will help physicians prescribe doses and drugs most likely to be effective in an individual.

Diet, activity and obesity: participants sought for survey

We are interested in studying some of the environmental factors that are interacting with genetics to influence disease risk inthe Personalized Medicine Research Project. Two environmental factors that we are particularly interested in are diet and physical activity. We are looking for PMRP participants who are interested in completing a diet and physical activity questionnaire so that we can better understand the relationship between these factors and genetics. We will compensate you for your time with a $10 payment. If you are enrolled in the PMRP and are interested in learning more about this project, please contact Yvonne Cerne at 715-387-9433 or toll free 1-866-293-1666, option 0.

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.

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