

Personalized Medicine

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Genetics and cholesterol

New study examines effectiveness of cholesterol-lowering medications

Marshfield Clinic is part of a large, multi-center research study designed to gain insight into ways that a person's genes alter his or her response to a specific group of cholesterol-lowering medications called "statins," which are typically used to prevent the onset or recurrence of heart disease.

The Pharmacogenomics and Risk of Cardiovascular Disease (PARC) project is examining variations in gene structure, known as polymorphisms, and determining which variations can be used to predict how well a person responds to the statins.



**Russell A. Wilke,
M.D., Ph.D.**

Russell A. Wilke, M.D., Ph.D., a pharmacologist with Marshfield Clinic's Center for Human Genetics, is one of several investigators on the \$14 million project, funded by the National Institutes of Health (NIH). Dr. Wilke received nearly \$1 million for his portion of the work. Marshfield Clinic is the only site studying the statin drug Lipitor (atorvastatin). Other statin drugs in the study include Zocor (simvastatin), Pravachol (pravastatin) and Crestor (rosuvastatin).

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MARSHFIELD CLINIC
Research Foundation

From the Director



Cathy McCarty, Ph.D.

Welcome to the second Personalized Medicine Research Project (PMRP) newsletter. We are thankful to our Community Advisory Group (see names listed

on the back of the newsletter) who provide us with content suggestions for the newsletter and ideas for the project in general.

Just as a reminder, the PMRP was designed to protect study subject confidentiality. The database for analysis does not have personal identifiers, which also means that study subjects will not receive personal genetic information

back from us. Instead, as study results become available, we will publish them in this newsletter.

A goal of researchers in the Center for Human Genetics is to have at least one research result translated into patient care by the year 2008 so that everyone will benefit. We sincerely thank all people who have chosen to participate in the PMRP! If you know anyone who would like to participate, please let them know that we are still enrolling subjects. They can stop by the Lawton Building at the Marshfield Clinic-Marshfield Center, or phone (888) 334-2232 or (715) 389-7733 to make an appointment.

Did you know that the PMRP is the largest population-based DNA bank in the entire

U.S.? Our researchers have been invited to give talks to the National Institutes of Health, the Centers for Disease Control and Prevention, and at research institutions in the U.S. and overseas, to describe methods used to successfully recruit nearly 19,000 people. With five projects underway using the PMRP database, we expect to receive national and international attention on central Wisconsin's contribution to understanding the genetic causes of Alzheimer Disease, osteoporosis, hypertensive heart disease and the genetic basis of response to cholesterol lowering and glaucoma medications. We hope to share some of these results with you in the next newsletter. How exciting to be a part of medical research history!

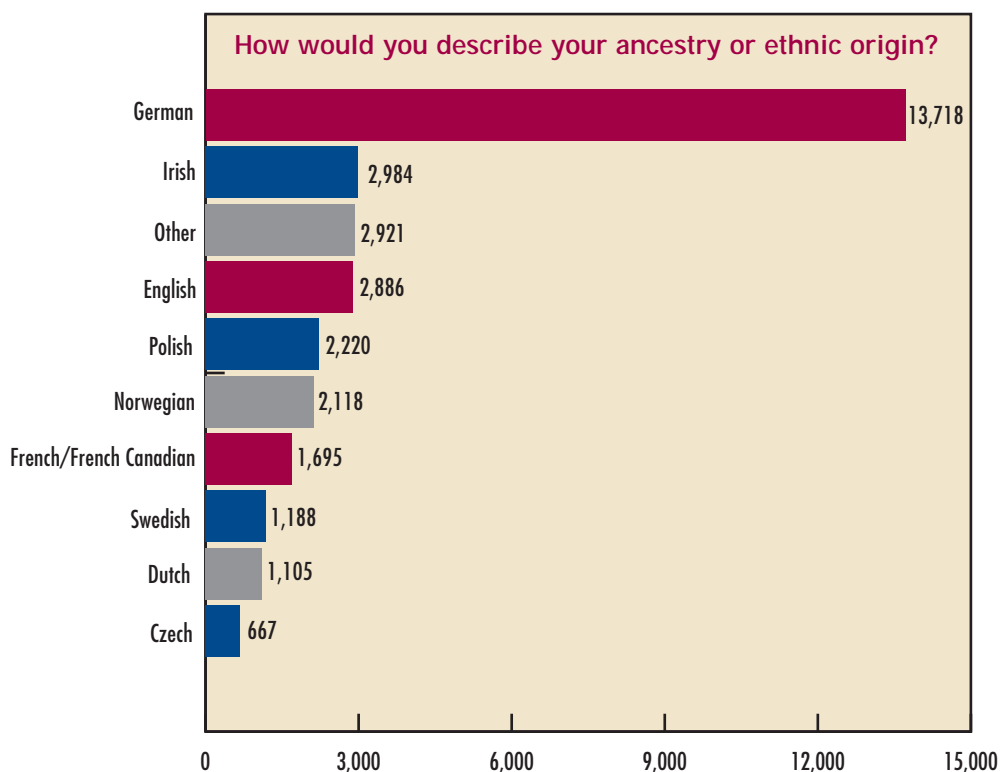
Did you know?

A total of 17,463 subjects were enrolled in the Personalized Medicine Research Project during the first 23 months of recruitment. Some facts regarding this group:

- The participants had an average age of 48.9 years.
- The majority of participants indicated that they had German ancestry (76.5%).
- The majority reported that their current area of residence was a suburb, city or village (60.9%); the remainder reported residence in a rural home or hobby farm (30.7%) or a working farm or ranch (8.3%).
- More than half (53.9%) had lived on a working farm at some point in their life.

German ancestry No. 1 among PMRP participants

Of the nearly 18,000 persons enrolled in the PMRP as of February 2005, 76.5 percent (13,718) reported German ancestry. Here is the complete breakdown. Participants could report more than one ethnic origin.



Osteoporosis project taps Personalized Medicine data

Osteoporosis affects approximately 1 in 5 postmenopausal females and accounts for approximately 1.5 million fractures in the United States annually. Both genetic and environmental factors are thought to contribute toward the development of osteoporosis.

Marshfield Clinic researchers are trying to understand how specific genetic factors involved in bone development may be associated with osteoporosis. Osteoporosis can be diagnosed in an individual that has sustained a “low energy” fracture of the hip, spine or distal forearm and/or if that individual had evidence for osteoporosis on a bone mineral density scan (DXA). Researchers are also trying to understand the interplay between these genetic factors and environmental factors such as cigarette smoking and use of cholesterol-lowering medications such as statins.

Nearly 9,000 of the almost 19,000 subjects in the Personalized Medicine Research Project (PMRP) Biobank have high cholesterol levels. Many of these subjects utilize statin drugs to lower their cholesterol. Since clinical studies conducted elsewhere have suggested that statin drugs

might alter a subject's rate of bone loss, Philip F. Giampietro, M.D., Ph.D., director, Marshfield Clinic Medical Genetics Services, plans to verify this on an unprecedented scale using the Biobank.



Philip Giampietro, M.D., Ph.D.

Using the PMRP database, researchers are linking an individual's genotype (internally coded, inheritable information) to a phenotype (observable traits such as the presence or absence of osteoporosis) and also consider the influence of environmental exposures (smoking and use of cholesterol lowering statin drugs, as

well as factors that contribute to maintenance of bone mass such as calcium and vitamin D).

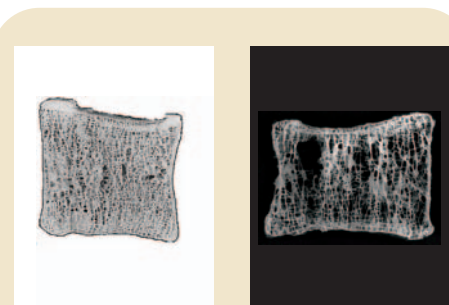
Researchers include: Dr. Giampietro; Cathy McCarty, Ph.D.; James LeVesseur; Fergus McKiernan, M.D.; Deborah Wilson, M.D.; Dick Berg, M.S.; and Terrie Kitchner.

“These study results may help us understand which combinations of genetic and environmental factors may predispose a person to the development of osteoporosis,” Dr. Giampietro said. “Study results can lead to increased bone density monitoring for those individuals who are at greater risk for developing osteoporosis and prevention strategies for avoidance of environmental risk factors. This study may also help determine if statin medications may help prevent osteoporosis.”

Subjects sought

The PMRP is recruiting subjects for this and other studies. We are particularly interested in recruiting healthy female subjects who are postmenopausal, do not have osteoporosis or osteopenia (based on a DXA scan performed within the last two years), and are not taking estrogen or other hormone replacement therapies.

Call 888-334-2232 or 715-389-7733.



Scan of a healthy bone (left) and an osteoporotic bone (right).

Enrollees sought for PMRP

Enrollment in the Personalized Medicine Research Project (PMRP) is open to anyone age 18 and over living in the following communities: Abbotsford, Arpin, Auburndale, Blenker, Chili, Colby, Dorchester, Granton, Greenwood, Hewitt, Loyal, Marshfield, Milladore, Pittsville, Spencer, Stratford, Thorp, Unity, Vesper.

Please call the PMRP at 888-334-2232 or 715-389-7733.

Personalized Medicine oversight committee named

A Personalized Medicine oversight committee has been developed to give the final review and approval or disapproval of studies that utilize the PMRP biological samples. The role of the committee is to choose projects that are important to making a difference to improve health care, approve non-reusable resource and give final approval for access to DNA, plasma/serum samples.

The committee includes: Humberto Vidaillet, M.D., chairman; Michael Caldwell, M.D., Ph.D., principal investigator; Philip Giampietro, M.D., Ph.D., chair of clinical genetics; Cathy McCarty, Ph.D., director, Center for Human Genetics; and Kurt Reed, M.D., director, Marshfield Laboratories.

PMRP scientists at Alzheimer's conference

Cathy McCarty, Ph.D., and Nader Ghebraniou, Ph.D., were on the agenda at the 20th annual State Conference on Alzheimer's Disease and Related Disorders, May 7-9, in Green Bay. Their talk was titled “Genetic and Environmental Contributions to Alzheimer's Disease: A study using the Marshfield Clinic Personalized Medicine Research Project Database.” Dr. McCarty and Dr. Ghebraniou quantified the relative impact of statin use, cigarette smoking, genetics and the interaction of environment and genetics on the development of Alzheimer's. For more information, visit the Alzheimer's Association of Greater Wisconsin Web site, <http://www.alzgw.org/>, or call (920) 469-2110.

Genetics and cholesterol

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Dr. Wilke and the Marshfield PARC team have two primary aims:

- Use the Personalized Medicine Research Project (PMRP) database to find genetic markers that predict changes in LDL cholesterol after patients take a statin drug.
- Enroll additional people who have taken one of three specific statin drugs – atorvastatin, simvastatin and pravastatin – then try to determine which genetic polymorphisms predict adverse drug reactions for these three statin drugs. Recruiting is underway.

“Discoveries such as these are likely to lead to gene-based statin prescribing at some point in the not-too-distant future,” Dr. Wilke said. “They may even allow clinicians to someday reduce the frequency of adverse drug reactions.”

The PARC team includes investigators at Harvard University, University of California at Los Angeles, University of Washington and Children’s Hospital Oakland Research Institute. The PARC study is currently one of five active research projects in the Center for Human Genetics using the Personalized Medicine Research Project database.

“The PARC study will give us answers, and we hope to be able to get those answers into clinical practice in five to 10 years,” said Cathy McCarty, Ph.D., director of the Center for Human Genetics. “Pharmacogenetics will change health care delivery soon.”

The Personalized Medical Research Project, the largest population-based genetic research study in America, has more than 18,000 participants. PMRP is the largest study undertaken at Marshfield Clinic.

Personalized Medicine is a publication of the Personalized Medicine Research Project, Center for Human Genetics, Marshfield Clinic Research Foundation, Marshfield, Wisconsin.

Contact the Personalized Medicine Research Project, 1000 N. Oak Ave., Marshfield, WI 54449-5790; phone 888-334-2232 or 715-389-7733; fax 715-389-4950; or visit our Web site at <http://www.marshfieldclinic.org/chg/pages/default.aspx>.

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