You’re invited to a celebration!

The Personalized Medicine Research Project (PMRP) recently enrolled its 20,000th participant. The nation’s largest population-based biobank is marking the milestone by inviting you to a special event.

Join us for appetizers and a short program with participants, media and the scientists who are translating genetic discoveries into new medications and diagnostic tests.

Date: Tuesday, May 18, 2010
Place: Robert F. Froehlke Auditorium
        Marshfield Clinic
        Marshfield, WI
Time: Program  5:30 – 6:30 p.m.
      Reception 6:30 – 7:30 p.m.

RSVP required as seating is limited to 150 guests. Please call 715-389-4478 by May 11 if you plan to attend.

The PMRP enrolled its first participant in 2002, dairy producer Sharon Bredl of Stratford. Since then, recruiting (persons 18 and older) has been focused on the 19 ZIP Codes around Marshfield.

DNA from our 20,000 participants forms a database enabling scientists to study which genes cause disease, which genes predict reactions to drugs, and how environment and genes work together to cause disease.

The goal of this project remains the same: to learn how to apply genetic science to human health. This knowledge will help researchers develop new medications.

Samples for 20,000 individuals have been processed as part of the Personalized Medicine Research Project, and enrollment continues. Any Marshfield Clinic patient who is 18 years or older and lives in one of the 19 ZIP codes around Marshfield can stop by the Lawton Center on the Marshfield campus, or call 1-888-334-2232.
The PMRP continues to receive attention at the national level and we can all be very proud of what we are doing here “in the middle of nowhere.” We were honored to be selected to present at a one-day symposium on biobanking in January that was organized by the new Director of the National Institutes of Health (NIH), Dr. Francis Collins. We were in good company, with speakers from the National Institutes of Health, the American Cancer Society, the UK BioBank in England, Vanderbilt University, the Centers for Disease Control and Prevention, and Kaiser Permanente. Information about this meeting can be found on the NIH web site and a summary paper is being written (http://commonfund.nih.gov/newmodels/).

Marshall Clinic Research Foundation and Security Health Plan belong to the Health Maintenance Organization Research Network (HMORN), comprised of researchers in 14 HMOs across the US. The mission of the HMORN is to integrate research and practice for the improvement of health and health care among diverse populations. The PMRP and Marshall Clinic were represented at a meeting with Dr. Francis Collins to discuss the potential of the HMORN to conduct large epidemiologic studies and clinical trials to improve health care delivery. More information about this initiative can also be found on the NIH web site (http://commonfund.nih.gov/hmocollaboratory/).

We had been invited previously to speak to the Department of Veterans Affairs Genomic Medicine Program Advisory Committee and I have been nominated to be a member of this committee. Information about this committee is available on the VA web site (http://www1.va.gov/advisory/docs/CharterGenomic2-12-2008.pdf).

All of this attention could not have happened without the participation of every individual in the PMRP. I want to thank you again for your support!

With all this attention to the PMRP, many scientists have approached us to collaborate on research projects. Our newest collaboration is with scientists at the University of California Irvine to investigate genetic predictors of low iron levels.

We welcome your feedback and questions. If you have suggestions for items for the newsletter or questions that you would like answered, please log onto our website at http://www.marshfieldclinic.org/chg. I look forward to updating you in person about some of the projects using the PMRP database at our May celebration. Look for details in this newsletter and RSVP quickly because space is limited.

From the Director

Project reaches 20,000 (continued from page 1)

and diagnostic tests, and will enable physicians to prescribe medications that work best for a particular person.

This concept of tailoring healthcare to an individual’s precise genetic profile is known as “Personalized Medicine.”

All 20,000 participants in the PMRP are making important contributions to science. Some genetic research projects are larger than the PMRP, but none combine the following elements as well:

- Electronic Health Record – Computerized record keeping captures all medical information on Marshfield Clinic patients, including lab results, consultations, procedures, diagnostic images and office notes. Only about 17 percent of the nation’s physicians are using computerized patient records.

- Health history – The average electronic health history for a PMRP participant goes back 30 years, longevity unmatched by any genetic research project in the world.

- A relatively stable population in terms of people moving into and out of the Marshfield Clinic service area. This makes long-term data collection easier.

Host for the celebration event will be Cathy McCarty, Ph.D., Principal Investigator of the PMRP. Dr. McCarty will introduce several speakers who will comment briefly on PMRP accomplishments:

Karl Ulrich, M.D., M.M.M., Marshfield Clinic President – What is personalized medicine? What does it mean to the Clinic, and where does it fit in the future of health care?

Adedayo Onitilo, M.D., Co-Investigator on the PMRP – Discovery of genetic variation that predisposes breast cancer patients to tamoxifen-caused blood clots.

Michael Caldwell, M.D., Ph.D., founder and former Principal Investigator of the PMRP – Development of a dosing calculator for a frequently prescribed blood thinner, warfarin.

Cathy McCarty, Ph.D.
Amber Johnson of Eau Claire believes in making a difference and sees the importance of personalized medicine.

The unassuming 18-year-old high school student has already earned a nursing assistant certification, so she is familiar with health and health care delivery. And she’s part of scientific research through her willingness to be a participant in several studies, the most important being a genetics project that could some day make a difference for many people around the world.

Johnson and a friend enrolled in the Personalized Medicine Research Project in late fall 2009, and by doing so she became the 20,000th person to participate in this landmark research.

“We are so grateful to Amber and everyone who chooses to participate in research projects,” said Cathy McCarty, Ph.D., Principal Investigator of the PMRP. “The more people who participate, the more information we will gather to benefit everybody.”

Marshfield Clinic researchers began recruiting voluntary PMRP participants in 2002. Recruiting originally focused on a 19-ZIP Code area surrounding Marshfield, but now individuals beyond that region have been invited to participate if they are at least 18 years of age, receive health care at any Marshfield Clinic location, and have a health care problem that is being studied.

Researchers use DNA, plasma, serum and tissue samples and data from electronic medical records to study how genes and environment are involved in disease. Why? If doctors can understand which genes and environmental factors are involved in a disease, they may be able to target the disease with specific medications. Also, this information might help doctors predict the risk of disease in an individual person and prescribe preventive measures.

Born in Superior, Wis., Johnson has lived in many places during her young life and it was when she recently lived in the Greenwood area, about a half hour west of Marshfield, when she first learned about the PMRP. Johnson and a friend “talked it over and thought it would be a good opportunity to help others learn about their health care and to make a difference.”

“It made perfectly fine sense” to Johnson and “my friend and I thought it was great.” Johnson is interested in how personalized medicine could help her with her health and is especially aware of health issues in her own family, like diabetes and acid reflux disease.

She plans to graduate in June from an Eau Claire high school and pursue a career in the human or veterinary health fields. But most important, she will also give birth to her son this summer.

“My baby is doing excellent and it’s a boy. Taking good care of myself is really important and maybe someday the contribution to this research could make a really big difference for my son.”

“Reaching this number of enrollees is a significant goal for the project,” she added. “The larger the number of people in this research study, the more confidential data researchers have to help advance science to benefit medicine and the care people will receive.”

Milestone Participants
1 – Sharon Bredl, Stratford.
5,000 – Jean Toltzman, Spencer
10,000 – Ethel Kramer, Stratford
15,000 – Gwen Steen, Dorchester
20,000 – Amber Johnson, Eau Claire
Studies utilizing the PMRP database

Genetic Terms

Genotyping: Determining genetic information for an individual. Genotype is the information about the gene form itself.

Phenotyping: Determining clinical information and characteristics about an individual. Phenotypes are observable traits such as hair color, weight, or the presence or absence of a disease.

SNP: An abbreviation for “single nucleotide polymorphism,” a small chemical change in a sequence of DNA.

GWAS: Genome-Wide Association Study.

Genetic Epidemiology

Genetic epidemiology evaluates the role of inherited causes of disease in families and in populations; it aims to detect the inheritance pattern of a particular disease, localize the gene and find a marker associated with disease susceptibility. Gene-gene and gene-environment interactions should also be studied in genetic epidemiology of a disease.

Diseases being studied

- Cataracts
- Low HDL levels
- Obesity, genetics and risk of diabetes and abnormal lipids
- Glaucoma
- Prostate cancer
- Cardiovascular disease
- Hypertensive heart disease
- Osteoporosis
- Alzheimer’s disease
- Fibromyalgia syndrome
- Heart attack

Genome-Wide Study of Cataract and Low HDL in the Personalized Medicine Research Project

Project leader: Catherine McCarty, Ph.D.
External collaborator: Russell Wilke, M.D., Ph.D., Vanderbilt University

The aim of this study is to develop and validate electronic phenotyping algorithms to identify cases of cataract and low-HDL (good cholesterol) in the PMRP, and also 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.

Obesity, Genetics and Lipids

Project leader: Catherine McCarty, Ph.D.
External collaborator: Russell Wilke, M.D., Ph.D., Vanderbilt University

About two-thirds of adults in the United States are either overweight or obese. This study seeks to evaluate five genetic markers to see if they predict who does or does not develop bad lipid (cholesterol and triglyceride) values among people who have a body mass index of 40 or greater.

The Role of PITX2 in Adult-Onset Glaucoma

Project leader: Catherine McCarty, Ph.D.
External collaborators: Elena Semina, Ph.D., and Linda Reis, M.S., C.G.C., Medical College of Wisconsin

PITX2 is a protein that is involved in the development of the eye, tooth and abdominal organs. This study seeks evidence to support or refute a role for PITX2 in causing adult-onset glaucoma.

Development of a Predictive Model for Clinically Relevant Prostate Cancer Using Genetic, Environmental, and traditional Risk Factors

Project leader: Deanna Cross, Ph.D.

This study uses prostate cancer as a model to determine if genetic information can indeed increase the ability to predict disease. The model performance will be compared to that of traditional PSA screening.

Identification and Validation of Protein Biomarkers for Cardiovascular Disease

Project leader: Deanna Cross, Ph.D.
External collaborators: Ted McClusky M.D., Ph.D., and Evangelos Hytopoulos, Ph.D., Aviir Inc., has verified the effectiveness of an algorithm for predicting myocardial infarction (heart attack). Given the underlying inflammatory biology of a variety of cardiovascular disease event types, Aviir believes that this test might be capable of also predicting the risk of those events.

The Role of Genetic Variation in the Vitamin D Receptor and Vitamin D Receptor-dependent Signal Transduction Pathways in the Onset and Progression of Hypertensive Heart Disease

Project leader: Catherine McCarty, Ph.D.
External collaborators: Robert Simpson, Ph.D., University of Michigan; Corinne Engelman, Ph.D., and Kristin Meyers, Ph.D., UW-Madison

Heart failure affects nearly 5 million people in the United States. This study concluded that genetic variation in vitamin D biosynthesis is associated with increased risk of heart failure. (Pharmacogenomics. 2009 Nov;10(11):1789-97.)

The Role of Cigarette Smoking, Statin Use and Genetics in the Development of Osteoporosis in Postmenopausal Women

Project leader: Philip Giampietro, M.D., Ph.D., UW-Madison
External collaborator: Alan Shuldiner, M.D., University of Maryland

Results: The women with osteoporosis differed from controls relative to body mass index, age, and smoking but not statin use. After adjusting for age, evidence suggested a role for genetic variation in two genes in conferring risk for osteoporosis in Caucasian women, with the latter manifest only in smokers. (Osteoporos Int. 2010 Mar;21(3):467-77.)

A Population-Based Study of Pharmacogenetics and Glaucoma

Project leader: Catherine McCarty, Ph.D.

The objective of the study was to identify genetic predictors of a positive intraocular pressure (IOP) response to beta-blocker eye drops. Researchers found that a coding single-nucleotide polymorphism is associated with an increased likelihood of a clinically meaningful IOP response to beta-blocker eye drops. These results have clinical relevance because eye drops are the least expensive class of agents used to lower IOP. Genotype-based drug prescribing could save health care dollars. (Arch Ophthalmol. 2008 Jul;126(7):959-63.)

Genetic and Environmental Contributions to Alzheimer Disease: Implications for Risk Assessment

Project leader: Catherine McCarty, Ph.D.

The focus of this study is to identify and phenotype a cohort of patients aged 65 years and older with Alzheimer’s disease among subjects enrolled in the Personalized Medicine Research Project.
**Evaluation of Possible Genetic Markers for the Fibromyalgia Syndrome**

Project leader: Jonathan Reeser, M.D., Ph.D.

Fibromyalgia is a chronic pain syndrome that is difficult to diagnose and treat. It affects millions of people in the United States. This study evaluates a possible genetic risk factor for fibromyalgia.

**Genetics of Myocardial Infarction and Clinical Cardiac Risk Factors**

Project Leader: Catherine McCarty, Ph.D.

The overall goals of this project is to determine whether genetic polymorphisms in two drug detoxification enzymes are associated with the risk of a delayed allergic reaction to the sulfonamide antibiotic sulfamethoxazole.

**Pharmacogenetics and Risk of Cardiovascular Disease (PARC)**

Project Leader: Catherine McCarty, Ph.D.

This landmark study is designed to show how genetic differences can influence a person’s response to the widely-used type of cholesterol-lowering drugs known as “statins.” PARC will also contribute to our growing scientific understanding of the cellular and molecular mechanisms of action for this class of drugs, as well as clarifying important related signaling pathways impacting clinical outcomes.

**Human Genetic Variation and Response to Metformin Therapy**

Project Leader: Catherine McCarty, Ph.D.

Diabetes has reached epidemic proportions. Some 90 percent of diabetes cases in the U.S. are Type 2, sometimes called “adult-onset” diabetes. One of the most widely prescribed drugs for the treatment of Type 2 diabetes is metformin. The PMRP is studying two genes that are believed to influence a patient’s ability to utilize metformin.

**Pharmacogenetics/Genomics**

Pharmacogenetics is the study of genetic changes as related to their responses to drugs/medications in humans or in laboratory organisms.

**Drugs being studied**
- Sulfa hypersensitivity
- Efficacy and safety of statins
- Efficacy of metformin to treat diabetes
- ACE inhibitors and angioedema
- Warfarin metabolism
- Tamoxifen and breast cancer
- Drug-induced adverse events

**Polymorphisms in Cytochrome b5 and its Reductase, and Risk of Sulfonamide Hypersensitivity**

Project Leader: Catherine McCarty, Ph.D.

The overall goal of this proposal is to determine whether genetic polymorphisms in two drug detoxification enzymes are associated with the risk of a delayed allergic reaction to the sulfonamide antibiotic sulfamethoxazole.

A Pilot Study on the Association Between Polymorphisms in Estrogen Receptor Genes and Clinical Outcomes in Breast Cancer Patients Receiving Tamoxifen Treatment

Project leader: Adedayo Onitilo, M.D.

Tamoxifen has been used in breast cancer treatment for more than 30 years and has saved the lives of many women. Unfortunately, tamoxifen can cause fatal blood clots in certain cases. In this study, researchers found the first evidence identifying which genetic variations predispose an individual to tamoxifen-caused blood clots. (Breast Cancer Res Treat. 2009 Jun;115(3):643-50. Epub 2008 Dec 12.)

**Proof of Concept: Application of Machine Learning to Identify Novel Parameters Associated with Susceptibility to Drug Induced Adverse Events**

Project leader: Michael Caldwell, M.D., Ph.D.

The goal of this project is to use healthcare information gathered in Marshfield Clinic’s electronic medical record and, by application of machine learning techniques, develop step-by-step problem-solving procedures (algorithms) and models that predict therapeutic outcomes and adverse healthcare events. Update: A paper was submitted to the Association for the Advancement of Artificial Intelligence conference, July 2010.
Why does research seem to take so long?

**PMRP access strictly controlled**

At the heart of the Personalized Medicine Research Project (PMRP) is its biobank. You can think of a biobank as a warehouse. It collects, stores, and processes data. It distributes biological materials and the data associated with those materials for research. The PMRP’s biological materials are specimens of DNA, blood and tissue. The data are the clinical information (diagnoses, lab results, etc.) of the donor of the biological materials.

Researchers use the biobank to answer questions about which genes may cause disease. They can use it to see which genes may potentially predict reactions to drugs. It can also be used to see how environment and genes work together to cause disease.

Access to the PMRP biobank is strictly controlled. All requests by researchers to use data and samples must go through several approval steps, which can take up to six months to complete.

**Feasibility**

The first step is to see if there are enough people in the PMRP to do the research. When a researcher makes a request to use PMRP data, Marshfield Clinic’s Information Systems conducts a computer search of the database. A researcher might ask how many people in the PMRP over the age of 50 have ever been tested for levels of iron in their blood? And of that group, how many had low or anemic levels?

**Scientific merit**

The next step is a Scientific Merit Review. This is done to make sure that there is scientific value to the research. Some research requests have been through scientific review outside of Marshfield Clinic. Examples of outside review include the National Institutes of Health and the National Science Foundation. Research requests that have not been through outside review must pass a review by the Marshfield Clinic Research Foundation Research Committee.

**Institutional Review Board**

Next, the proposal goes to Marshfield Clinic’s Institutional Review Board, or IRB. This board is made up of medical professionals and lay members. Under Food and Drug Administration regulations, an IRB monitors research involving human subjects. An IRB makes sure that appropriate steps are taken to protect the rights and welfare of subjects in the research. An IRB looks at how the research will be done and the materials used, including the recruitment information and the informed consent. They also do reviews throughout the research study.

The final step is the Oversight Committee, made up of physicians, scientists and staff. Their role is to make certain the proper Scientific Merit and IRB reviews were done. They have the final say on whether a project can use the PMRP database.

**Research begins**

After all approvals have been completed, the research can begin with phenotyping. Phenotypes are the physical traits of an individual. As in the Feasibility stage, a research coordinator will ask the Clinic Information Systems to search the database for participants with certain physical traits. These could be traits like high blood pressure, diabetes or low blood iron levels. The difference this time is that the request will include Medical History Numbers of individuals. The research coordinator must make sure that what the computer search showed, and what the medical record says, match. For example, if a medication was prescribed we want to make sure that the chart also indicates that the medication was taken.

Once the subjects that will be included in the research are found, they are coded with study ID numbers and are given to the research lab. The lab will pull the samples and prepare them for genotyping. Genotyping is determining the genetic code of the DNA.

To maintain privacy and confidentiality, the Medical History Numbers are removed and the data are coded when phenotyping is complete. They are then put together with the coded genotypic data. At this point, the data are finally ready for transfer to the researcher.
2001
The Personalized Medicine Research Center is established within Marshfield Clinic Research Foundation under the direction of Michael Caldwell, M.D., Ph.D., and Steve Wesbrook, Ph.D. “Given the resources of Marshfield Clinic, the concept of the Personalized Medicine Research Project was a fairly simple one,” Dr. Caldwell said. “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.”

2002
Enrollment begins for the Personalized Medicine Research Project.

Cathy McCarty, Ph.D., is appointed Director of the Personalized Medicine Research Center.

2003
10,000th participant enrolled.

Francis Collins, M.D., Ph.D., Director of the National Human Genome Research Institute, refers to the PMRP and provides a link to its Web site in an article that he wrote for the journal Nature.

The PMRP is cited in the New England Journal of Medicine as an excellent example of a large-scale genetics research project.

2004
15,000th participant enrolled.

The Personalized Medicine Research Center is merged with the Center for Medical Genetics to form the Center for Human Genetics. In the new center resides the Personalized Medicine Research Project.

Studies are underway on multiple sclerosis, amyotrophic lateral sclerosis, prostate cancer, warfarin dosing, Alzheimer’s disease, hypertensive heart disease, scoliosis, osteoporosis, statins and muscle damage, glaucoma and age-related macular degeneration.

2005

Marshfield becomes an active site in the National Institutes of Health-funded multicenter project, “Pharmacogenomics and Risk of Cardiovascular Disease.” The project is designed to clarify the role of genetic variation in differential responses to statin drugs, used to control cholesterol levels.

Cathy McCarty, Ph.D., is named Interim Director of the Center for Human Genetics.

2006
A breast cancer pharmacogenetics research program is developed.

2007
The PMRP begins its largest research study to date, “Genome-Wide Study of Cataract and Low HDL in the Personalized Medicine Research Project,” funded by the National Institutes of Health’s National Human Genome Research Institute. PMRP researchers begin collaboration with four other sites to form a consortium to evaluate how biobanks attached to electronic medical record systems can be used for large-scale genetic research. This consortium is known as the eMerge Network.

The PMRP is asked to join the Pharmacogenetics Research Network (PGRN).

2008

The first published results of a study involving the PMRP identify a gene associated with positive response to the most inexpensive class of drugs prescribed for lowering pressure in the eye, topical (eye drop) beta-blockers.

2009
Gov. Jim Doyle announces the Wisconsin Genomics Initiative (WGI) on October 10 in Marshfield. The WGI involves the PMRP, Medical College of Wisconsin, University of Wisconsin School of Medicine and Public Health, and UW-Milwaukee.

The Center for Human Genetics moves into office and lab space in the new Laird Center for Medical Research.

2009
Murray Brilliant, Ph.D., is named the inaugural James Weber Endowed Chair and Director of the Center for Human Genetics.

20,000th participant enrolled.

PMRP Timeline
Collaboration vital to genetics research

The PMRP collaborates with other institutions to maximize the strengths of each. Marshfield’s collection of DNA and health data provides a wealth of information, while Medical College of Wisconsin has one of the country’s top human genetics labs. UW possesses supercomputers to help process the vast data, and UW-Milwaukee’s urban health programs will help expand the knowledge base beyond the rural PMRP. “With our combined knowledge, expertise and technologies here in Wisconsin, we have an incredible opportunity to become a worldwide leader in personalized health care,” Doyle said.

The Wisconsin Genomics Initiative is another example. Announced in October 2008 in Marshfield by Gov. Jim Doyle, the success of the initiative depends on the strengths of each partner. Marshfield’s collection of DNA and health data provides a wealth of information, while Medical College of Wisconsin has one of the country’s top human genetics labs. UW possesses supercomputers to help process the vast data, and UW-Milwaukee’s urban health programs will help expand the knowledge base beyond the rural PMRP. “With our combined knowledge, expertise and technologies here in Wisconsin, we have an incredible opportunity to become a worldwide leader in personalized health care,” Doyle said.