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Marshfield Clinic
Research Foundation

Personalized Medicine Research Project

New study probes patient and physician opinions on using genetic data

Pharmacogenomics is the study of how a person's genes (DNA) affect their body's response to medications. It is the hope that drugs will one day be chosen for people based on their own genetic makeup. Incorporation of Pharmacogenomics into the Electronic Medical Records (PGx) is the name of the new research project soon to be enrolling participants at Marshfield Clinic Research Foundation. This new genetic study is being done to help understand how genetic information can affect the medical care of patients.

Researchers will use the genetic results from people that take part in the project and place it in the patients' medical records. The hope is for doctors to use the genetic information when prescribing certain medicines to help take the guesswork out of finding the right drug for the right person. Pharmacogenomics has the potential to reduce the estimated 100,000 deaths and 2 million hospitalizations each year in the United States caused by an adverse drug response. Researchers will also study how doctors use this information.

"This project is really important because it will show how genetic information can help a doctor treat a patient with medicines that are best suited to the patient," said Cathy McCarty, Ph.D., the Principal Investigator of the eMERGE grant. Murray Brilliant, Ph.D., is the co-Principal Investigator who will oversee the project at Marshfield Clinic Research Foundation. The eMERGE network is funded by the National Human Genome Research Institute (NHGRI) and includes nine sites across the US (www.gwas.net).

Last summer, Marshfield Clinic patients and doctors from Family Practice and Internal Medicine took part in discussion groups. These discussion groups were very helpful in learning how patients and doctors feel about genetic testing. Both patients and providers feel that genetic research could lead to better patient care. They agreed that it would be useful to know ahead of time which drugs work best for patients. All group participants had some concerns that the use of genetic test information in medical practice could do harm as well as good.

Patients said benefits and risks must be weighed when using genetic testing in medical care. Their main concern was the risk of being treated unfairly by insurance companies and employers based on genetic test results. They also said knowing that a genetic health problem may occur in the future could be a positive to some people and a negative for others. "Those are important concerns and all future research must address those concerns," noted Murray Brilliant, Ph.D.

Patients believed that the choice to get a genetic test will vary from person to person and

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Inside

From the Director, Center for Human Genetics

Murray Brilliant, Ph.D.

In addition to the NHGRI-funded, national eMERGE network (see article on first page), PMRP is a key resource for two large research networks in Wisconsin: the Wisconsin Genomics Initiative (WGI) and the Institute for Clinical Translational Sciences (ICTR). The Wisconsin Genomics Initiative (WGI) is a historic collaboration between Marshfield Clinic, Medical College of Wisconsin, University of Wisconsin School of Medicine and Public Health, and University of Wisconsin-Milwaukee. WGI resulted from $2 million in support from the state of Wisconsin and a challenge to the four institutions to leverage their resources to advance genomic research for Wisconsin and the nation. WGI aims to predict a person's risks of disease and response to treatment by looking at their genetics, medical tests, and lifestyle. Together, the four WGI partners have begun work on important scientific and public health needs that otherwise could not be met, and cannot be accomplished anywhere else but Wisconsin. PMRP has been used to develop ways to predict which people are more likely to develop diseases such as Age-related Macular Degeneration, Atrial Fibrillation/Flutter, Aortic Aneurysm, Cardiac complications from Diabetes, Venous thromboembolism, and for better tests for Breast Cancer.

The Institute for Clinical Translational Sciences (ICTR) has recently been awarded $41,549,200 from the National Institutes of Health (NIH). ICTR is a partnership between the UW Schools of Medicine and Public Health, Pharmacy, Nursing, Veterinary Medicine, and the College of Engineering, and Marshfield Clinic. PMRP is a key resource of ICTR and a major reason that the award was given. PMRP data has been used in ICTR studies to better understand the most common form of mental retardation in boys (Fragile X syndrome) and the relationship between oral and systemic health (see related article). Indeed, my recent presentation to the scientists and physicians on the External Advisory Committee for ICTR was greeted with both envy and amazement. Your participation in PMRP has led to past advances in medical research and has paved the way for future studies. Thank you!

From the eMERGE Principal Investigator

Cathy McCarty, Ph.D.

Greetings from Duluth!

As I write this column, I am in my final week of my forties and a mystery "Nifty at 50" mug appeared on my desk! I received a birthday letter from Essentia Health, my employer and health care provider here in Duluth, with the greeting "Dear Friend" and information about colon cancer screening when I hit this milestone birthday. Colorectal cancer is one area where personalized medicine is already occurring. I don't have a family history of colorectal cancer but if I did my physician would have recommended that I get my first screening earlier than age 50 or perhaps have a genetic test. For people with a diagnosis of metastatic colorectal cancer, genetic testing of the tumor is used to help determine the best chemotherapy. Researchers at Marshfield have been involved with personalized medicine research for both colorectal cancer screening and treatment.

The eMERGE network (www.gwas.net) has been very active and we are contributing to most of the network activities. Our site is taking the lead on creating the computer code to identify people with and without ocular hypertension and glaucoma so that we can combine data across the network to identify genetic predictors of those two eye diseases. We are also developing tools so that information collected at eye exams is entered into the electronic medical record making it easier to use in the future for both clinical and research purposes. These tools will be shared with other eMERGE sites. Much of our success in eMERGE I was due to Carol Waudby. Carol was the Lead Research Coordinator for eMERGE from the beginning of the project in 2007. She left us recently to join her husband in Fargo where he is working. We miss Carol and wish her the very best in this next chapter of her life!

As always, thanks to all of you for your support of the Personalized Medicine Research Project. A quick glance in this newsletter at the funding source for a number of the projects using the database shows that donors to the Marshfield Clinic Research Foundation make a major contribution to our science. And of course, none of the science could happen without the people who chose to participate in the project. Thank you one and all!

Family history helps us to know about our chances of getting disease

Deanna Cross, Ph.D.

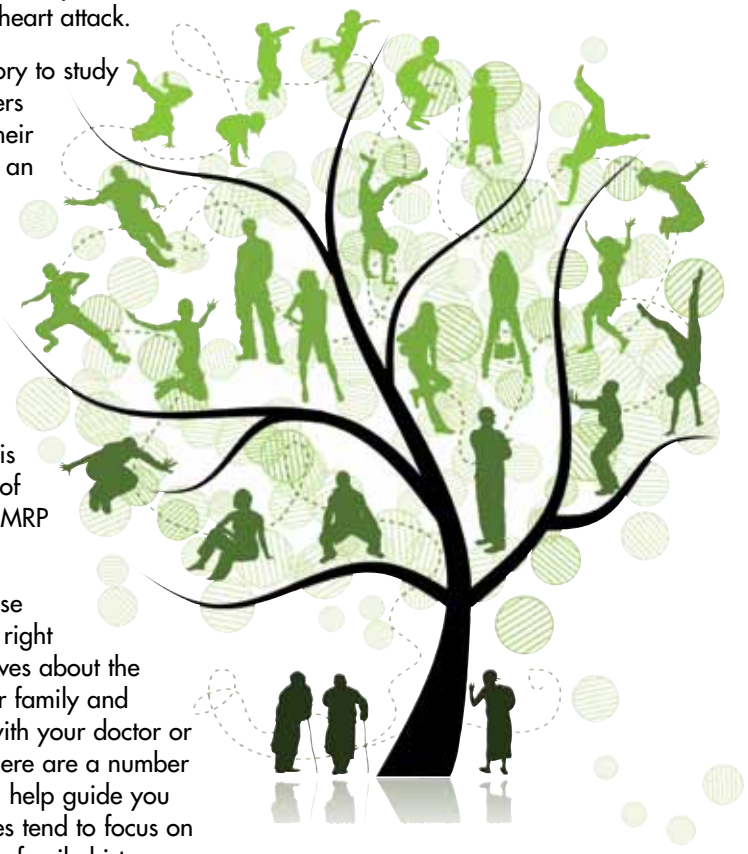
When you offered to be in the PMRP study, you filled out a questionnaire that asked if you or your family members had certain diseases. We call this information family history and use it in our genetic studies in a number of different ways. The reason family history can tell us about disease is the same reason that family members often look like one another; they share DNA (known as genes) which determines how our body looks and functions. As an example, in my family almost everyone has a heart attack. This means I am more likely to get a heart attack than someone from a family whose members do not have heart attacks. Because family history tells us about the diseases that we share with our families, we can use it to make our genetic studies better.

We can use family history as a standard to compare what we know about disease genes. We did this for a study of heart attacks. We tested a few genes that are known to increase heart attack risk and also checked family history to see which is better at predicting who will get a heart attack. We found that a family history of heart attack was a better way to find out who would have a heart attack than using any single or combination of the genes we tested. This is probably because we haven't found all of the genes that cause heart attack yet and family history tells us a little bit about all the genes in a person and how they work together.

We also use family history to help us find new genes that cause disease. We can study families that have many persons affected with a certain disease, like my family and heart attacks, to find the genes that cause the disease. To do this we look for genes that are found in the family but are rarely found in the general population.

An example of such a study is one we are doing with Dr. Uli Broeckel at the Medical College of Wisconsin. In this study, we have looked at all of the genes in over 40 people in the PMRP who did not seem likely to have a heart attack but did indeed experience a heart attack. These people were chosen partly because they have a family history of heart attack. The results of this study are not complete but the first set of results does look like we can identify some new rare genes that may increase the chance of having a heart attack.

We also use family history to study how health care providers choose medicines that their patients should take. As an example, we found that people with a family history of heart attack were more likely to take drugs that lower cholesterol than people with no family history of heart attack. We are planning to study this more in a larger group of people who are in the PMRP population.



Here's a way you can use your own family history right now! You can ask relatives about the diseases that run in your family and write it down to share with your doctor or health care provider. There are a number of free websites that will help guide you to do this. These websites tend to focus on diseases where we know family history is important. In the box below, we've provided the web address to several of these sites.

Websites to help you create a family health history

United States Surgeon General's website
https://familyhistory.hhs.gov/fhh-web/home.action

Health Heritage
http://healthheritage.ddig.com/

Utah Department of Health
http://health.utah.gov/genomics/familyhistory/documents/Toolkit/new%20entire%20toolkit.pdf

http://healthfamilytree.utah.edu/

Genetic Alliance
http://www.familyhealthhistory.org/

Centers for Disease Control and Prevention
http://www.cdc.gov/genomics/famhistory/famhist.htm

Studies utilizing the PMRP database

Genetic Terms

Genotyping: The process of finding out the genetic make-up of a person. Genotype is the information about the gene itself.

Phenotyping: The process of finding out clinical information about a person. Examples of phenotypes are hair color, weight, or the presence or absence of disease.

SNP: An abbreviation for "single nucleotide polymorphism", a small change in the base units that make up DNA.

GWAS: Genome-Wide Association Study. These studies look across a person's entire DNA as opposed to looking at one section of DNA, such as a gene.

Cardiovascular disease

Cardiovascular disease is a class of diseases that involve the heart or blood vessels (veins and arteries). Many studies using the PMRP database aim to find out what increases the chances of getting cardiovascular disease.

A multi-institutional cohort to investigate promising biomarkers for cardiovascular disease prediction (Cardiovascular Research Network)

Project leader: Deanna Cross, Ph.D.
Collaborator: Catherine McCarty, Ph.D., Essentia Institute of Rural Health; Porat Erlich, Ph.D., Geisinger Health System
Funding: National Heart, Lung and Blood Institute

New tools need to be developed to better predict who will develop cardiovascular disease. The goal of this study is to create a multi-center study population, describe the cardiovascular disease risk profile of the population, and determine if additional biomarkers would help doctors and patients to better determine how to decrease heart attack risk with either behavioral or drug interventions.

Genome-Wide Association Study of Coronary Artery Disease in the Personalized Medicine Research Project

Project leader: Ulrich Broeckel, M.D., Medical College of Wisconsin
Collaborators: Deanna Cross, Ph.D. and Humberto Vidaillet, M.D., Marshfield Clinic
Funding: National Heart, Lung and Blood Institute

The objective is to perform a genome-wide association study to identify susceptibility genes for coronary artery disease, myocardial infarction and its related risk factors. This study will improve our understanding of the interplay of genetic and traditional risk factors in coronary artery disease.

WGI Exome Sequencing to Identify Coding Variants for Myocardial Infarction

Project leader: Ulrich Broeckel, M.D., Medical College of Wisconsin
Collaborators: Deanna Cross, Ph.D., Marshfield Clinic; David Page, Ph.D., UW-Madison
Funding: Wisconsin Genomics Initiative

A myocardial infarction is another name for a heart attack. The exome is the portion of our DNA that codes for genes. The aim is to sequence 40 PMRP participants that have been diagnosed with myocardial infarction but did not have the normal risk factors for heart attack, to identify the genetic variants that are most likely to be associated with this disease.

Genetics of Myocardial Infarction and Clinical Cardiac Risk Factors

Project leader: Deanna Cross, Ph.D.
Collaborators: Humberto Vidaillet, M.D., Marshfield Clinic; Catherine McCarty, Ph.D., Essentia Institute of Rural Health; Russell Wilke, M.D., Ph.D., Vanderbilt University

Funding: Philanthropic gifts in support of medical research at Marshfield Clinic

The overall goal is to test whether SNPs on chromosome 9p21 affect the risk of myocardial infarction in a number of independent populations. We also aim to investigate the role of risk factors such as hypertension, diabetes, and hypercholesterolemia and their treatment in conjunction with these newly identified risk SNPs.

Membrane metaloproteinase-9 genotype and aortic aneurysm (Wisconsin Genomics Initiative)

Project leader: Peggy Peissig
Collaborators: Jay Yang, M.D., Ph.D., UW School of Medicine and Public Health; Ulrich Broeckel, M.D., Medical College of Wisconsin; Martha Wynn, M.D. and Sijian Wang, Ph.D., UW-Madison
Funding: Wisconsin Genomics Initiative

Aortic aneurysm is a swelling of the aorta, the main blood vessel that carries blood from our heart to the rest of our body. The goals are to identify the subset of subjects in the PMRP database with a well-established clinical workup and longitudinal data on the progression of aortic aneurysm, to determine the allele frequency and linkage disequilibrium of membrane metaloproteinase-9 SNPs of the subjects and matched controls, and to develop a statistical model predictive of rapidly progressing aortic aneurysms requiring surgical or endovascular intervention.

Identification and Validation of Protein Biomarkers for Cardiovascular Disease (Aviir)

Project leader: Deanna Cross, Ph.D.
Collaborators: Catherine McCarty, Ph.D., Essentia Institute of Rural Health; Ted McClusky, M.D., Ph.D., and Evangelos (Vangelis) Hytopoulos, Ph.D., Aviir
Funding: Aviir

Aviir Inc. has verified the effectiveness of a formula for predicting myocardial infarction. 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 aim is to test the Aviir algorithm on the PMRP database. This study developed a new risk scoring system based on measuring protein levels in blood and other clinical factors, and showed that this scoring system was useful for determining the true risk of cardiovascular disease in patients who were previously classified has having moderate risk. (Curr Med Res Opin 2012 Nov;28(11):1819-30.)

The Role of Plasma Vitamin D and Genetic Variation in Vitamin D Pathways in the Onset and Progression of Hypertensive Heart Disease: A follow-up study in the Marshfield Personalized Medicine Research Project

Project leader: Deanna Cross, Ph.D.
Collaborators: Richard Dart, M.D. and Richard Berg, Marshfield Clinic; Catherine McCarty, Ph.D., Essentia Institute of Rural Health; Corinne Engelman, Ph.D., and Kristin Meyers, Ph.D., UW-Madison
Funding: Philanthropic gifts in support of medical research at Marshfield Clinic; Clinical and Translational Science Award through UW – Institute for Clinical and Translational Research

The objective of this study is to investigate the relationship between vitamin D levels, genetic variations in the vitamin D pathway, and hypertensive heart disease.

Other Chronic Diseases

Chronic diseases are diseases that last a long time and that generally develop very slowly. Examples of these diseases are heart disease, stroke, cancer, and diabetes. These diseases cause most of the deaths around the world. Researchers are using the PMRP database to find out the causes of chronic diseases.

Development of a Predictive Model for Clinically Relevant Prostate Cancer Using Genetic, Environmental, and Traditional Risk Factors (Cancer Research Network)

Project leader: Deanna Cross, Ph.D.
Collaborators: Douglas Reding, M.D., Marshfield Clinic; Catherine McCarty, Ph.D., Essentia Institute of Rural Health
Funding: National Cancer Institute

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. It has found that survival for prostate cancer patients treated at Marshfield Clinic follow national trends. (Clin Med Res. 2012 Aug;10(3):97-105.)

Development of an Individualized Risk Assessment for Secondary Complications of Radiation Therapy for Prostate Cancer

Project leader: Deanna Cross, Ph.D.
Collaborators: Catherine McCarty, Ph.D., Essentia Institute of Rural Health; Mark Ritter, M.D., Ph.D., and Amy Moser, Ph.D., UW – Madison; Murray Brilliant, Ph.D., Marshfield Clinic
Funding: Clinical and Translational Science Award through UW – Institute for Clinical and Translational Research

This study uses clinical and genetic information to determine if we can predict who may suffer long term side effects from radiation treatment for prostate cancer. In the end it seeks to develop a risk score that could be used by people to help them better understand the likelihood of side effects before treatment so they can make informed treatment decisions.

Molecular Markers for Non-Small Cell Lung Cancer Susceptibility

Project leader: James Burmester, Ph.D.
External collaborator: Jill Kolesar, Pharm.D., UW-Madison
Funding: UW Carbone Cancer Center

The aim is to find genetic markers that predict the risk of getting lung cancer. Genetic material (DNA) from non-small cell lung cancer subjects will be compared to DNA from subjects who do not have cancer. Differences in the DNA patterns between the two groups may be a marker of lung cancer risk.

Integrating Genomic Data into a Computational Model for Improved Breast Cancer Diagnosis

Project leader: Catherine McCarty, Ph.D.
Collaborators: Peggy Peissig and Adedayo Onitilo, M.D., Marshfield Clinic; Elizabeth Burnside, M.D. and David Page, Ph.D., UW-Madison; Ulrich Broeckel, M.D., Medical College of Wisconsin
Funding: Wisconsin Genomics Initiative

This Wisconsin Genome Initiative pilot proposal aims to incorporate genetic polymorphisms with the risk factors that radiologists observe including the shape and margins of masses, the shape and distribution of micro-calcifications, and background breast density (all promising biomarkers for stratifying risk), as well as known demographic risk factors to improve risk prediction for breast cancer.

A Pilot Study of Age-Related Macular Degeneration in PMRP

Project leader: Murray Brilliant, Ph.D.
Collaborator: Catherine McCarty, Ph.D., Essentia Institute of Rural Health
Funding: Philanthropic gifts in support of medical research at Marshfield Clinic

The goal is to develop a predictive formula for age-related maculation degeneration using data from previous association studies and biological samples from the PMRP database.

Phase II – Predicting and Preventing Age-Related Macular Degeneration

Project leader: Murray Brilliant, Ph.D.
Collaborators: David Page, Ph.D., UW-Madison; Joseph Carroll, Ph.D., Medical College of Wisconsin
Funding: Wisconsin Genomics Initiative

The purpose of this study is to determine a predictive formula for those at high relative risk for age-related macular degeneration (AMD) based on previously identified genetic markers, age, sex, environmental factors and advanced retinal imaging. Prediction of AMD with high accuracy will allow for future therapies to be targeted to specific people and hopefully allow us to prevent AMD before it occurs.

Genome-Wide Study of Cataract and Low HDL in the Personalized Medicine Research Project (eMERGE I) and Incorporating Research into Sight (eMERGE II)

Project leaders: Catherine McCarty, Ph.D.; Murray Brilliant, Ph.D.
Collaborators: Russell Wilke, M.D., Ph.D., Vanderbilt University; Norman Frost, M.D., UW-Madison; Marylyn Ritchie, Ph.D., Penn State University
Funding: National Human Genome Research Institute

eMERGE I: The aim of this study is to develop and validate electronic phenotyping formulas to identify cases of cataract and of reduced high density lipoprotein cholesterol (HDL-cholesterol or 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 reduced HDL-cholesterol are two yet interrelated diseases. Update: This study has developed an approach to identify cataract cases using electronic health records. In addition, it has also shown that certain changes in the CNR1 gene appear to have a protective effect on the decrease in HDL cholesterol concentrations that typically accompanies weight gain. It has also shown that the LPL and ABCA1 genes are both involved in regulating HDL-cholesterol concentrations.

eMERGE II: This study will develop ways to use electronic medical records to identify cases of certain eye diseases. These diseases include ocular hypertension (the pressure inside the eye is higher than normal), glaucoma (damage to the nerve that carries information from the eye to the brain), age-related macular degeneration (disease that causes loss of central vision leaving only side vision intact), and tear film insufficiency (the eye does not produce enough tears to keep it moist).
(BMC Ophthalmol. 2011 Nov;11:32. PLoS One 2010 Dec 31;5(12):e15779. PLoS One 2011 May;6(5):e19586.)

Metanomics Health and Marshfield Type 2 Diabetes Prediction

Project leader: Steven Schrodi, Ph.D.
Collaborators: Dietrich Rein, Ph.D. and Inken Padberg, Ph.D., Metanomics GmbH
Funding: Metanomics GmbH

About 90 percent of diabetes cases in the U.S. are Type 2, sometimes called "adult-onset" diabetes. This study will be used to replicate an existing metabolite-based predictive model for Type 2 diabetes. The study will also incorporate data from an exome-based GWAS and from metabolic/inflammatory biomarkers to improve Type 2 diabetes prediction.

Protein Tyrosine Phosphatase, Non Receptor Type 22 (PTPN22) Phenomics

Project leader: Steven Schrodi, Ph.D.
Funding: Philanthropic gifts in support of medical research at Marshfield Clinic

Among persons with European ancestry, the PTPN22 gene has a SNP (known as R620W) that is related to the chances of getting a number of diseases. Many of these diseases involve inflammatory processes (a group of processes that the body uses to protect itself when there is an infection). Some of these diseases are type 1 diabetes, rheumatoid arthritis, and bacterial infections. The aim of this study is to find new diseases that are related to R620W. By discovering new relationships between R620W and disease, researchers can find out more about the role that the PTPN22 gene plays in human health.

Pharmacogenetics/ Genomics

Pharmacogenetics is the study of how genes are related to a person's response to drugs/medicines.

Genome Wide Association Study to Identify Genetic Predictors of ACE Inhibitor Associated Angioedema

Project leader: Catherine McCarty, Ph.D.
Collaborators: Nancy Brown, M.D., Vanderbilt University; Marylyn Ritchie, Ph.D., P
enn State University
Funding: Pharmacogenomics Research Network of the National Institute of General Medical Sciences

ACE inhibitors are drugs used to treat high blood pressure. About 35-40 million people worldwide use these drugs. ACE inhibitors can also cause harmful effects in some persons who use these drugs. One such harmful effect is angioedema, a serious reaction involving swelling of the face, hand, or other parts of the body. Angioedema can cause a person to be admitted to hospital and can even lead to death. This study will try to identify what makes a person more likely to get angioedema after using ACE inhibitor drugs.

A Pilot Study for the Identification of Severe Cutaneous Reactions and Genomic Risk Factors in Users of Anti-Epileptic Drugs

Project leader: James Burmester, Ph.D.
Collaborators: Robert Davis, M.D, Center for Health Research Southeast; Nandini Selvam, Ph.D., HealthCore; Maryam Asgari, M.D., Kaiser Permanente; Melody Eide, M.D., Henry Ford Health Services; David Margolis, M.D., University of Pennsylvania
Funding: US Food and Drug Administration

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis are two forms of a life-threatening skin condition in which cell death causes the top layer of the skin (epidermis) to separate from layers underneath (dermis). The aim is to identify patients at Marshfield Clinic with Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis and to estimate the number of cases that are potentially available for possible future research studies. The project will also genotype 100 random DNA samples from the PMRP population and determine the frequency of the HLA-A*3101 and HLA-B*1502 alleles.

Genotype and Clopidogrel/Proton Pump Inhibitor Interactions

Project leader: Amanda Hein, M.D.
Collaborators: James Burmester, Ph.D. and Michael Caldwell, M.D, Ph.D., Marshfield Clinic
Funding: Philanthropic gifts in support of medical research at Marshfield Clinic

Clopidogrel is a medication used to prevent strokes and heart attacks in patients at risk for these problems. Proton pump inhibitors are a group of medications used to reduce the amount of acid produced by the stomach. By using a clearly defined and stable epidemiologic research population, the goal is to analyze phenotypic and genotypic data of a subset of PMRP participants for possible Clopidogrel/proton pump inhibitor interactions that may ultimately change the course of medical management for the cardiac and vascular patient populations.

Human Genetic Variation and Response to Metformin Therapy

Project leader: Melissa Simpson, D.V.M., Ph.D.
Collaborators: Catherine McCarty, Ph.D., Essentia Institute of Rural Health; SookWah Yee, Ph.D. and Kathleen Giacomini, Ph.D., University of California – San Francisco; Robert Davis, M.D, Center for Health Research Southeast; Russell Wilke, M.D., Ph.D., Vanderbilt University
Funding: Agency of Healthcare Research and Quality; Pharmacogenomics Research Network of the National Institute of General Medical Sciences; RIKEN Institute

Metformin is a drug used to treat diabetes. The goal is to assess whether single nucleotide polymorphisms in the OCT1 and/or OCT2 genes are more frequent among metformin-exposed subjects with type 2 diabetes who did not respond to metformin compared with metformin-exposed subjects with type 2 diabetes who were responsive to metformin.

PGPop: PharmacoGenomic Discovery and Replication in Very Large Patient Populations

Project leader: Murray Brilliant, Ph.D.
Collaborators: Peggy Peissig, Marshfield Clinic; Dan Roden, M.D., Michael Stein, M.D., Dana Crawford, Ph.D., Hua Xu, Ph.D., and Joshua Denny, M.D., Vanderbilt University; Marylyn Ritchie, Ph.D., Penn State University
Funding: Pharmacogenomics Research Network of the National Institute of General Medical Sciences

The aim is to establish a research network to study patient data on how drug (medicine) exposures are related to disease outcomes. The first studies will examine how certain drugs affect patients with asthma.

Other Genetic Epidemiology Studies

Genetic Epidemiology is the study of the interaction between genes and environmental factors in causing disease in human populations and their patterns of inheritance in families.

Prevalence of the Fragile X Premutation

Project leader: Murray Brilliant, Ph.D.
Collaborators: Elizabeth McPherson, M.D., Marshfield Clinic; Marsha Mailick, Ph.D. and Matthew Maenner, Ph.D., Waisman Center, UW-Madison; Mei Baker, M.D., Wisconsin State Laboratory of Hygiene and UW-Madison.
Funding: US Centers for Disease Control and Prevention

Fragile X is a genetic condition involving changes (mutations) in the FMR1 gene on the X chromosome. It is the most common form of inherited mental retardation. Some people may only have a small change in their FMR1 gene (called a pre-mutation) and may not show any signs of Fragile X. Other people may have bigger changes in the gene, called a full mutation, that cause the symptoms of Fragile X syndrome. The goal is to identify Fragile X full mutations and pre-mutations in the PMRP population.

Th17 Activity Genome-Wide Association Study

Project leader: Steven Schrodi, Ph.D.
Funding: Philanthropic gifts in support of medical research at Marshfield Clinic; Clinical and Translational Science Award through UW – Institute for Clinical and Translational Research

T helper 17 cells (Th17) are a group of cells in the immune system. They are thought to play a key role in autoimmune diseases (when the body attacks itself), such as multiple sclerosis and rheumatoid arthritis. The objective is to discover genetic regions that segregate alleles associated with the activity of the IL-23/IL-17 pathway as mediated through Th17 cells.

Nonsense SNP Phenomics

Project leader: Scott Hebbring, Ph.D.
Collaborators: Murray Brilliant, Ph.D., Marshfield Clinic; David Page, Ph.D., UW-Madison
Funding: Philanthropic gifts in support of medical research at Marshfield Clinic

A nonsense SNP is a small change in DNA that causes only a portion of a protein to be made. Because only part of the protein is made, the protein is not able to perform its functions within our bodies. This study is designed to identify common diseases, defined by medical diagnosis codes, which are associated with nonsense SNPs in genes that have been linked to specific human diseases.

Validation of PhenX Measures in the Personalized Medicine Research Project for Use in Gene/Environment Studies

Project leader: Catherine McCarty, Ph.D.
Collaborators: Murray Brilliant, Ph.D., Marshfield Clinic; Marylyn Ritchie, Ph.D., Penn State University
Funding: National Human Genome Research Institute

The aim is to have PMRP participants fill out the PhenX Toolkit questionnaire and compare the answers to those in other PMRP questionnaires previously completed by participants. Some of the questions are about age, weight, family history of heart attack, alcohol use, smoking, and amount of time spent in the sun. The answers to the questions will be checked to see if they are the same across different questionnaires. If they are the same, it means that the PhenX Toolkit questionnaire can be useful in collecting information about factors that affect our chance of getting disease.

Replication Analysis Dupuytren's Single-Nucleotide Polymorphism

Project leader: Eric Anderson, D.O.
Collaborators: Michael Caldwell, M.D., James Burmester, Ph.D., and Rama Mukherjee, M. D., Marshfield Clinic
Funding: Philanthropic gifts in support of medical research at Marshfield Clinic

Dupuytren's Disease is an abnormal thickening of the tissue just beneath the skin. Some persons with this disease develop severely bent fingers. This study tested the Dupuytren's Disease cohort for a mitochondrial mutation that was reported by other researchers and found that no one in the cohort had the mutation. This calls into question the role of this mutation in Dupuytren's Disease. (Clin Med Res. 2012 Aug; 10(3):122-6.)

Oral Systemic Research Project (OSRP) Pilot

Surgeon General David Satcher's report entitled "Oral Health in America" released in 2000, focused attention on a national problem which had gone largely unrecognized for decades: the oral health crisis. It also highlighted a silent epidemic of oral disease among populations with poor access to dental care. Now thirteen years later the oral disease burden is still a leading concern with costs and repercussions that go beyond oral health.

For decades now the medical community has known connections exist between oral diseases, such as periodontal disease and systemic diseases, such as diabetes, rheumatoid arthritis and cardiovascular diseases. Much more research is needed in this area, however, and given that treatment of periodontal disease may ease the burden of systemic diseases, this is a worthwhile area to focus attention and resources. Medical dental research is one of the national priorities identified in the U.S. Department of Health and Human Services' Healthy People 2020 plan and is a focus for the Marshfield Clinic.

As a new addition to PMRP, the Center for Human Genetics has been enrolling an additional group of clinic patients with dental specimens linked to both medical and dental records for oral systemic research. Knowledge gained from this work will be used to guide clinical practice (both dental and medical). The participants are part of a small pilot project. Pilots help researchers to know whether a project is feasible (can be done) and test processes (how it's done) so that the project can be designed well on a large scale.

During May-August 2012 we enrolled 41 subjects aged 45-74 years into a new research program known as the Oral Systemic Research Project (OSRP) Pilot. Subjects were enrolled at the Marshfield and Chippewa Falls dental clinics. To participate, subjects had to agree to enroll in the PMRP, if not previously enrolled. Blood, urine, saliva, and dental plaque specimens were collected and a short questionnaire was completed. These activities will be repeated once more when the subjects return for a follow-up dental appointment six to twelve months after their initial visits. The first follow-up appointment took place in November and we expect to complete the remainder by August 2013.

So far the pilot has shown us that, in general, the population is interested in participating in oral systemic research. Not only have people enrolled, but during recruitment several people expressed positive support for this area of study. The pilot has also helped us to identify ways that we could better carry out this project on a large scale in the coming months.

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Patient and physician opinions on using genetic data in patient care

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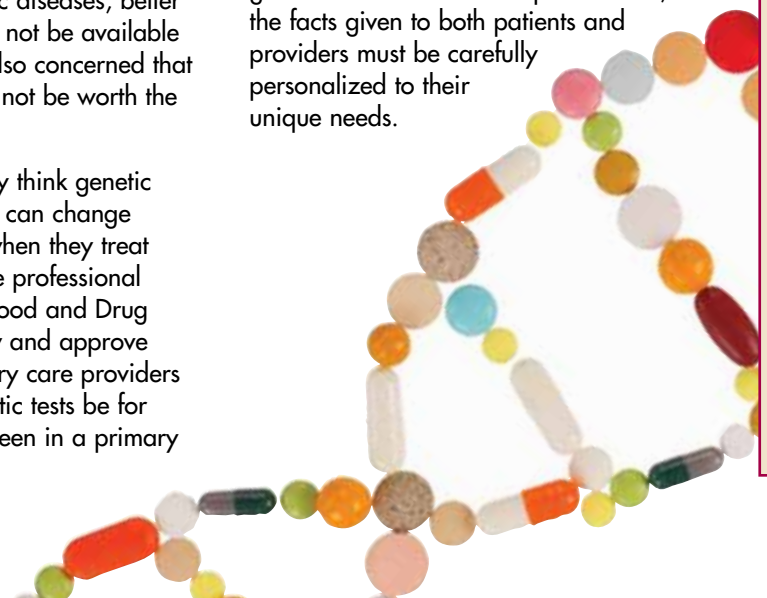
depend on a number of factors. They said that they are more likely to choose to get a genetic test if the disease is serious, if an effective treatment is available, if the test results are accurate, and if the disease is common in their family. Other factors such as cost and treatment, whether the test is covered by insurance, whether they trust their doctor, the influence of other people they know, and religious beliefs will affect people's choice to be tested.

Primary care providers are not sure how useful new genetic tests would be in their practice. They stated that although genetic testing will provide more information about the risks of genetic diseases, better treatments will probably not be available to patients. They were also concerned that benefits to patients may not be worth the cost to patients.

Providers stated that they think genetic information is useful if it can change the choices they make when they treat patients. They would like professional organizations and the Food and Drug Administration to review and approve new genetic tests. Primary care providers preferred that new genetic tests be for diseases that are often seen in a primary practice. They said that these new tests should provide great benefits to patients.

Discussions in the five groups led to a number of recommendations about patient and provider needs for genetic information. Patient information should include very brief and basic definitions to help patients understand genetics. Tools should be created to provide patients with information about genetic testing and be reviewed with patients to address their specific questions.

In summary, the thoughts of both patients and providers show that in order to use genetic research results in patient care, the facts given to both patients and providers must be carefully personalized to their unique needs.



Contact Us

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