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Marshfield Clinic
Research Foundation

Personalized Medicine Research Project

PMRP and eMERGE Network consider returning genetic results to study participants

The Personalized Medicine Research Project (PMRP) has been part of the Electronic Medical Records and Genomics (eMERGE) Network since 2007. The network, funded through the National Human Genome Research Institute, encourages rapid sharing of resulting data with the broad scientific community.

While this sharing of de-identified data has advanced science and health care, it also raises a question: what about the return of results to individual participants in genome-wide association studies (GWAS)? What ethical issues must be discussed?

The five biobanks that initially made up the eMERGE Network (www.gwas.net) formed a committee to explore the implications. PMRP members of this committee were Catherine McCarty, Ph.D., Carol Waudby and Marylyn Ritchie, Ph.D. The committee's findings are described in a recent journal article. Committee members agreed that the return of results should be considered only if risk for a disease is strongly affected by the presence of a genetic variant, and if there is the potential to change immediate medical care.

The committee found that most results from genome-wide association studies do not meet these criteria, but some may.

The committee selected four diseases for which there is the potential for return of results and used them to generate discussion about related medical and ethical issues. The diseases were Turner Syndrome, Klinefelter Syndrome, hemochromatosis and Factor V Leiden. Turner Syndrome and Klinefelter Syndrome are sex chromosome abnormalities that affect females and males, respectively, causing infertility and often times other physical problems. Hemochromatosis is associated with risk of excessive deposit of iron in body tissues and organs, with accompanying complications. Factor V Leiden causes excessive clotting in the veins.

At each of the five biobanks, study participants with the relevant genetic variants indicating increased risk for these diseases were identified. Their electronic medical records were reviewed to

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How do genes and environment play a role in cataracts? PMRP questionnaires may hold answers.

From the Director, Center for Human Genetics

Murray Brilliant, Ph.D.

The information we have learned from PMRP is population based and, under the terms of your consent, cannot be used to inform you as an individual about your own health risks. Your participation in PMRP has provided a treasure-trove of information on the genetic contribution to health and disease, allowing us to better predict who is at risk for specific diseases, who best benefits from specific treatments and who should, or should not, take specific drugs. The data gained from PMRP and other studies now allows us to predict how you as an individual will respond to certain drugs, i.e., will the drug work well for you without major side-effects.

We are about to launch a new research study (funded by the National Institutes of Health) aimed at testing individuals for gene variants that predict how you would respond to several specific drugs, including the commonly prescribed drugs, Warfarin (Coumadin), Clopidogrel (Plavix) and Simvastatin (Zocor).

Our plan is to recruit up to 750 Marshfield Clinic patients who are likely to be prescribed one of these drugs in the next few years. We will then look for variants associated with activity, dosing ranges and adverse reactions for drugs that are within FDA guidelines. Once a participant in this study is prescribed one of these drugs, your physician will see a message specific for you and that drug: i.e., that you are expected to respond normally to the drug along with a recommended dose or that you are at risk for an adverse drug reaction and an alternative medication may be indicated. We expect to begin recruitment for this project called "PGx" sometime this fall.

From the eMERGE Principal Investigator

Cathy McCarty, Ph.D.

As I mentioned in my last column, I moved to Duluth last June to accept a scientist position at Essentia Institute of Rural Health. I was born and raised in Duluth. I had the great fortune to spend some wonderful time with my Mom here in Duluth before her death on May 1. She was proud of my work as a scientist and when she developed an adverse reaction to an antibiotic in the hospital she asked me if it was genetic. I miss my Mom and I'll miss sharing our science with her. I am who I am because of her.

In my last column I mentioned that two new sites had joined the eMERGE Network, funded by the National Human Genome Research Institute. At our next Steering Committee meeting, we will be introduced to two more new sites. These sites are joining the network because they have pediatric populations.

I was asked to speak about the eMERGE Network at a meeting about personalized medicine held in Florence, Italy, in February. Participants were particularly impressed by the use of information from the electronic medical records to conduct valid genetic research.

As part of the PhenX RISING Network that makes use of the genetic data from eMERGE I, more than 2,000 of you completed a 30-page questionnaire that you received from us in the mail. Thank you so much for your time! This research network also includes seven sites and our site was the first one to complete data collection. We are just starting to analyze the data and will be looking for gene/environment interactions that increase a person's risk of cataract.

Deanna Cross, Ph.D., and I were asked to be part of an expert panel to advise the Centers for Disease Control and Prevention on various aspects of a biorepository for amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's Disease). Panel members were particularly enthusiastic about the ongoing communication with the PMRP participants through this newsletter.

We thank the editorial staff as well as our Community Advisory Group members who suggest items for the newsletter. If you have ideas for articles that you would like to see in your newsletter, please let us know!

PMRP data network is being upgraded!

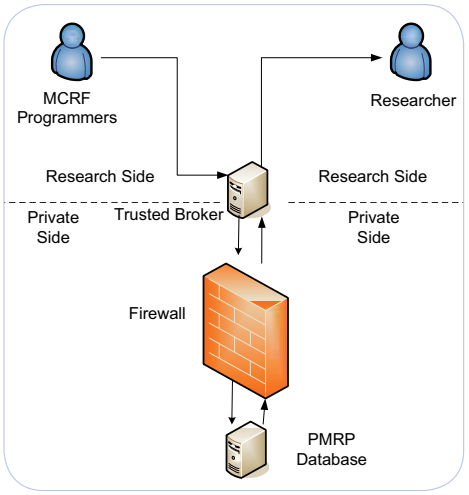
As part of our constant quest to make the Personalized Medicine Research Project better we are making some changes to the PMRP database. These improvements will allow us to support future needs as we move into exciting new realms of genetic research. Genetic data is drastically increasing in volume. Our analysis of data for each person has increased from a few thousand data points to billions of data points. It is now necessary to make changes to the PMRP computer system in order to allow us to move and store this data efficiently. These changes will also provide even better security over your research data than ever before. We have had the modifications reviewed by an independent consultant and by research advisory bodies to ensure that your privacy is protected. Thank you for your contributions to this important research!

Background

The PMRP network was originally set up as a private stand-alone network that is inaccessible from the rest of the Clinic network. Data is transferred to/from the PMRP network via a portable USB drive. But it is cumbersome, if not impossible, to move large data files to/from the PMRP network with the current design. As we move into the realms of whole-exome, and later full-sequencing, the amount of data that will be moved, stored, and manipulated on the PMRP network will increase exponentially.

Solution

The PMRP private network will be connected to the Clinic network through a state-of-the-art firewall appliance. This will allow for even greater security and the ability to move extremely large data to/from the PMRP network.



Researchers work off same page with new toolkit

PhenX (pronounced Phoenix), www.phenx.org, was developed as a way to promote research across multiple institutions. The PhenX toolkit helps investigators design or expand genomics-based studies by providing agreed-upon questions for data collection of phenotypes and exposures. When different research groups use the same questions it allows them to more easily work together on projects.

As Dr. McCarty mentioned in her column in this issue, PMRP is part of a group of seven sites that have used PhenX measures. Questions from the toolkit were combined into a questionnaire and mailed to over 3,000 PMRP participants. An impressive 70 percent of the questionnaires were returned. PMRP researchers are now analyzing the data to see how genes and the environment may play a role in cataracts.

The environmental exposures being looked at for risk of cataract development include smoking, sun exposure and whether a person is left- or right-handed. Smoking and amount of time spent in the sun are believed to increase the chance of getting cataracts and in developing them earlier in life. Handedness may factor into which eye would require surgery first.

The PMRP questionnaire also included questions about where parents and grandparents were born, birth order, housing, alcohol use, depression, and family history of heart attack. These will be factors considered in future research projects. They will also allow for comparison of PMRP findings with those of other research groups that have made use of the questions recommended through PhenX.

Thank you for your on-going participation in PMRP and your willingness to respond to questionnaires. This research cannot be done without you.

Director of Center for Human Genetics promotes oral and systemic health research

Dr. Murray Brilliant, Director of Center For Human Genetics, was invited to represent the Marshfield Clinic on December 5 – 6, 2011, at "Genomic Medicine II" the second in a series of meetings organized by the National Human Genome Research Initiative (NHGRI) to help the Institute identify future translational research priorities in genomic medicine. His presentation on the Oral Systemic Health Research Project of the Marshfield Clinic was well-received and several groups (Geisinger, Penn Dental School, University of North Carolina, and Mt. Sinai) expressed interest in working with researchers at the Marshfield Clinic to study the role of genetics and periodontal health on complex disorders such as type 2 diabetes. Dr. Brilliant was asked to lead a working group on this collaborative effort that will hopefully lead to future targeted funding by the NIH.

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determine if they had ever been diagnosed with the disease during the course of their non-study-related medical care. The review of medical records indicated that most study participants had not been diagnosed, and therefore were unaware of their genetic results with regard to these diseases.

Each biobank varied in its decision-making regarding whether to return results. At one biobank, the participants were made anonymous and it was impossible to identify and contact them. At other biobanks, concerns were expressed about the informed consent procedures for study participation and the logistics of returning the results.

Only one biobank had allowed for return of results. Other biobanks had stated to participants at study enrollment that there would be no return of results; therefore, new informed consent procedures would need to be approved. There is also an implied responsibility on the part of the biobank with the return of results to individuals. This led the biobanks to consider resources available for genetic counseling for participants and support for doctors regarding the use of the genetic information for making decisions in clinical practice.

Because of the varied circumstances facing each biobank, the committee thought that the final decision about returning results should rest with the local institution. The committee also recognized that sufficiently compelling results should merit consideration for return to participants because the medical risks of not disclosing the result are high.

The committee acknowledged that more research into the return of genetics results is needed. It also said there should be consistent involvement of community representatives in the process, something PMRP already emphasizes with its Community Advisory Group.

"Community engagement has been very important to us in the planning and implementation of the PMRP biobank," Dr. McCarty said. "We have had, and will continue to have, discussions with our Community Advisory Group about the best way to return genetic research results to study participants. Currently that is not possible because of the consent form that everyone signed before participating in the PMRP."

"Return of individual research results from genome-wide association studies: experience of the Electronic Medical Records and Genomics (eMERGE) Network," Stephanie M. Fullerton, et al. Genetics in Medicine. 2012;14:424-431.

Contact Us

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