

Personalized Medicine Research at the Marshfield Clinic

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Objectives

1. To describe the Marshfield Clinic Personalized Medicine Research Project
2. To describe studies using the biorepository
3. To describe challenges to implementation of study results into clinical practice



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Personalized Medicine Research Project

Ultimate Goal:

- Translate genetic data into specific knowledge about disease that is clinically relevant and will enhance patient care

Short term Goal:

- Establish database to allow research in genetic epidemiology, pharmacogenetics, population genetics

Sampling Frame

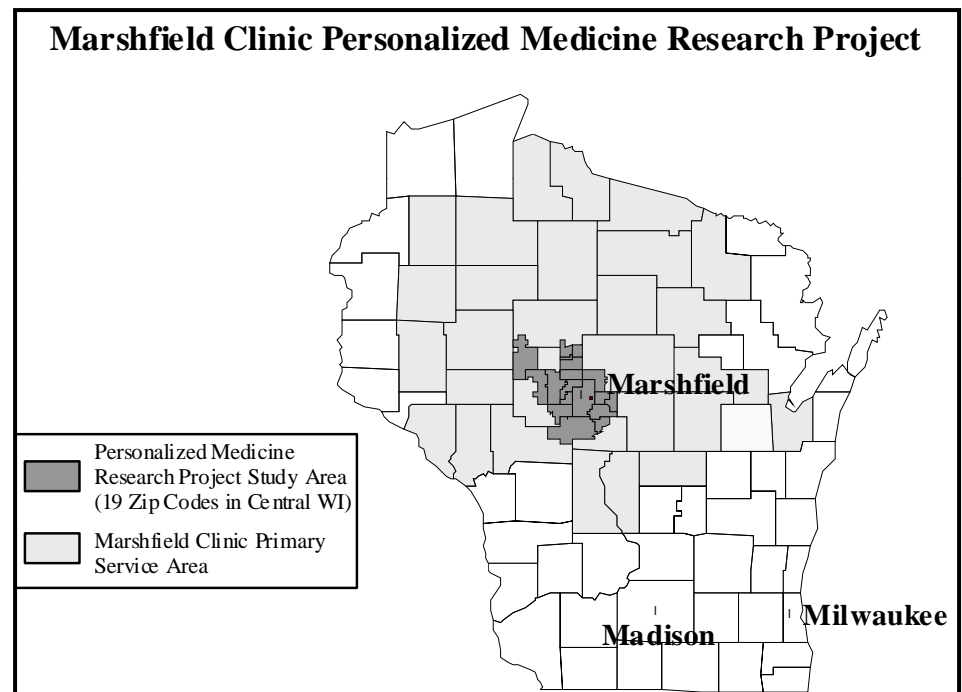
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Epidemiologic Study
Area (MESA)

96% of health events
captured

55% belong to health
plan

45% participation



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Consultation/Education

- Community Advisory Group
- Scientific Advisory Board
- Ethics and Security Advisory Board
- Focus group discussions
- Community talks
- Media releases
- Video for waiting rooms
- Employee newsletter
- Grand Rounds
- Annual primary care provider conference



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Planning Focus Groups, 2001-02

Purpose: consider project, materials

Conducted off-site by outside agency

Separate focus groups for employees

Over arching themes:

- Trust in the Marshfield Clinic
- Opposition to human cloning
- Concern about insurance discrimination
- Confidentiality of data, particularly clinical data (MC employees especially concerned)
- Some would never participate regardless

Recommendations: Security, simple materials



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2003 Focus Group Results

2 primary concerns:

- Time to learn/enroll
- Confidentiality (especially for employees)

Perception: little or no benefit for time

No or little awareness of PMRP

Suggestions: more concise information, more money

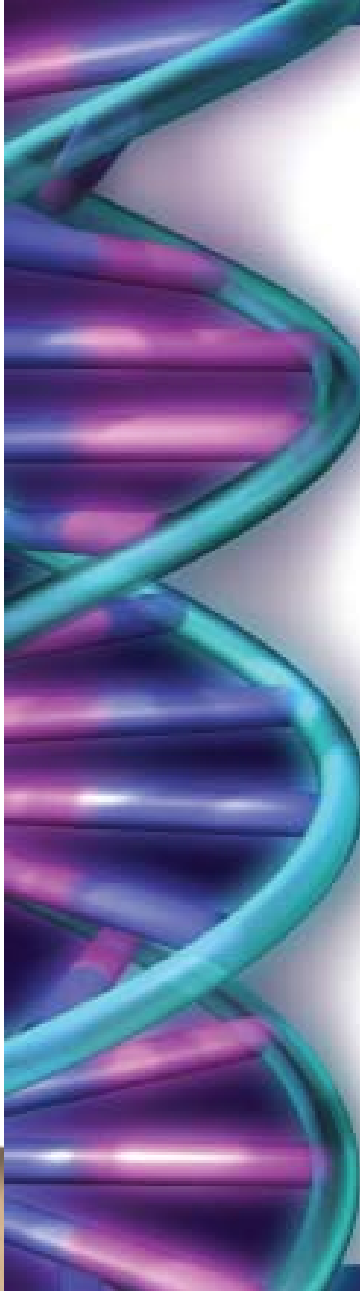
Response: new recruitment materials



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Newspaper insert



RESEARCH HAS LONG BEEN THE BASIS FOR IMPROVING MEDICINE AND HEALTH CARE

- In as little as 30 minutes, you can contribute to medical research.
- You will be compensated \$20 for your time.
- Over 14,000 central Wisconsin residents have already enrolled.


WHAT IF, IN THE FUTURE, YOUR DOCTOR COULD:

- prevent or detect which illnesses you or your family have or are likely to get and design a personalized health care plan to diagnose and treat early
- diagnose diseases accurately and use medications and other treatments that would work best for each individual
- treat appropriately, avoiding medications that would cause you to have bad side effects

If you are 18 or over and living in one of these 19 ZIP codes you are eligible.

54405	54420	54437	54454	54484
54410	54421	54441	54466	54488
54412	54425	54446	54771	54489
54415	54436	54449	54479	

If you would like to learn more about Marshfield Clinic's Personalized Medicine Research Project, what it is and is not, and how to participate, ask your health care provider or call **715-389-7733** or toll free at **1-866-394-2232** to talk with one of our research coordinators. Appointments are not necessary. Walk-ins are welcome.



"When I found out about the personalized medicine program, I saw the project as a good thing for the future. If participating benefits someone down the line, we should be doing these things. It goes hand in hand with what we do here at the Pittsville Fire Department. We help people. There is some personal satisfaction in helping people."

— Jim Glavin

(Back row) Jim Glavin, Bob Hill
(Front row) Larry Hill, Jerry Moss, Paula Hensell

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Where the future of medicine lives

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Community Advisory Group

20 members

Initially 18-month appointments that were extended

Selected to represent various demographics

Compensation: travel, stipend

Meet 2-5 times per year

Provide advice on all aspects of the project



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Discussion About Access to Stored Pathology Samples

Initial surprise by CAG that samples are stored for 25 years

Consent form specifies blood, not other tissues

Newsletter item written about access to stored samples mailed in early January

- Unanimous support to access personal samples

Applied for and received a waiver of informed consent



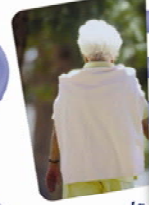
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Personalized Medicine

Summer 2007



Inside

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- Question & Answer 3
- How do residents most likely to say 'yes' to PMP enrollment 3
- In the media 3
- How informed are those who give informed consent? 3
- Peer-reviewed publications 3

Alzheimer's Personalized

It is estimated that by 2025 the U.S. population will be aging rapidly, and the prevalence of Alzheimer's disease is expected to increase significantly. Currently, there is no cure for Alzheimer's disease, but "there are many programs that might help delay the onset of the disease," says Dr. Gladstone, Ph.D., head of Molecular Diagnostic Laboratory.

Inside

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- Enrollees sought for PMP 3
- Personalized Medicine oversight committee named 3
- PMP scientists to present at Alzheimer's conference 3



Personalized Medicine

Summer 2007



Genetics and

New study examines effect of genetic factors on health outcomes. Marshfield Clinic is part of a multi-center research study to gain insight into ways that genetic factors or hereditary conditions called "genes" typically used to prevent the occurrence of heart disease.

Inside

- From the Director 2
- At-home genetic tests can have unintended consequences 2
- Diet survey shows area residents light on dairy products 3



Personalized Medicine

Winter 2007 • Volume 2, Number 1



Study targets possible genetic risk for fibromyalgia

Fibromyalgia is a chronic pain syndrome that is difficult to diagnose and treat. The fibromyalgia syndrome (FMS) affects millions of people in the United States. Fibromyalgia is among the most common conditions treated by rheumatologists and physical medicine specialists.



James Messer, M.D., Ph.D., notes that the diagnosis of the condition is often difficult to make. In fact, in fact, for many years there was considerable disagreement among clinicians over the issue of whether fibromyalgia was even "real."



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Discussion Related to Accessing Excess Clinical Samples

Logistics

- No record of PMRP participation in EMR
- Samples are discarded after 5-7 days

Current consent does not address additional samples

- Apply for waiver of consent
- Reconsent

CAG overwhelmingly supportive

Joint CAG/ESAB Meeting

Focused on the issue of access to prospective residual clinical blood samples

CAG very supportive

- Don't waste money
- If they would be thrown away anyway, use them for science

ESAB mixed

- "Slippery slope"
- Discussion about whether risk is increased
- Surprise at overwhelming community support

Recommendation: letter to all subjects with study update, opt out model for the project and residual clinical blood samples, ability to opt in to newsletter

Study Logistics

- MESA residents aged 18+ contacted
- Written informed consent
 - Allows for sharing de-identified samples and data
- Questionnaire
 - Demographics, smoking, alcohol, family history, employment, relationships in the cohort
- Measure height and weight, blood pressure
- DNA extraction, storage of plasma and serum
 - \$20 reimbursement for expenses
- Dietary history questionnaire, Baecke physical activity questionnaire added in 2008 (\$10)



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PMRP Summary

- Population-based biobank with > 20,000 adults
 - Average clinical history 29 years
 - Age 18-102, 57% female
- DNA, plasma and serum samples
- Molecular fingerprint with 36 medically-relevant polymorphisms
- Whole phenome panel with 15 additional markers
- Dietary intake and physical activity questionnaires
- Access to medical records
- Ability to recontact subjects
- GWAS available for 4200 subjects aged 50+



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Genetic Epidemiology Projects

- Alzheimer's Disease
- Multiple sclerosis
- Vertebral malformations
- Fibromyalgia syndrome
- Osteoporosis
- Cataract and low HDL
- Hypertensive heart disease
- Glaucoma
- Myocardial infarction
- Coronary artery disease
- Dyslipidemia in severely obese subjects
- Endometriosis
- Obesity
- Prostate cancer

Diabetic retinopathy



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Myocardial Infarction (MI)

3 chromosome 9 SNPs

Replicate previous GWAS findings

Update Framingham 10-year MI/coronary death risk score

- Age, gender, total cholesterol, HDL cholesterol, smoking status, systolic blood pressure, BP meds

Consider other clinical data available in the EMR and questionnaire data

- Diet and activity, family history, CRP, BMI

Implications: more aggressive treatment if markers impact 10-year risk



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Pharmacogenetics Projects

Warfarin

LDL response to statins

Topical beta-blockers for glaucoma

Metformin for diabetes

Tamoxifen in breast cancer

Delayed reactions to sulfonamides

ACE and angioedema

Response to asthma medications



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Glaucoma Pharmacogenetics

Study Question: What is the role of genetics in intraocular pressure response to topical β -blockers?

- Cost implications

Funding: American Health Assistance Foundation



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Study Design

Identify PMRP subjects with POAG or ocular hypertension

Abstract medical records for agents to lower IOP, all IOPs, concomitant medications

Genotype subjects who had ever used β -blockers for CYP2D6 (pharmacokinetic) and β -adrenergic receptor (pharmacodynamic) genes, as well as genes associated with glaucoma

Compare genotypes by 20%+/- drop in IOP



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Results

2.07% POAG, 1.42% ocular hypertension

253 subjects prescribed β -blockers

- 51% had 20%+ decrease in IOP
- 59% female, 41% male

CYP2D6, optineurin, myocillin not associated with IOP response

ADRB2 SNP associated with IOP response
(OR=2.41, 95%CI=1.00, 5.82)



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Implications of Findings

2 million people in the US have POAG

- Expected to grow to 3 million by 2010

Generic β -blockers cost between US\$0.38 and US\$0.50 per day

Prostaglandin analogs cost between US\$0.90 and US\$1.25 per day (2.4 to 3.3 times as much as generic β -blockers)

- Initial therapy of choice

Huge potential health care savings

Next Steps

Patent pending – alternative revenue

Evaluating prostaglandin analogs

Assess affect in other ethnic groups

Prospective study

Health economic modeling

Genetics of glaucoma

- Target for drug development



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Process to Access Samples

Feasibility request for phenotype

Scientific merit review

- External peer-reviewed funding mechanism OR Marshfield Clinic Research Committee

IRB review/approval for all studies

Oversight Committee to release samples

Funding is required for phenotyping and identification and retrieval of samples

Data deposit within 6 months after completing analyses



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Lessons Learned

Controls are more difficult to identify with EMR data than cases

Infrastructure funding is a challenge

Multi-disciplinary collaborations are key

Technology is changing rapidly

Informatics research and support need to keep pace with genetic technology for discover and translation

Ongoing community consultation at all levels is essential

It is more efficient to collect information up-front



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Challenges to Implementation of Personalized Health Care

Research funding

Time for physicians to be involved in research

Third party payer acceptance

Lack of outcomes data

Longer term returns, i.e. competing incentives

Electronic medical records

Informatics tools for analysis and decision support



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Wisconsin Genomics Initiative

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MCRF

- Rural Cohort Comprised of 20,000 Adults
- Biomedical Informatics
- Phenotyping

MCW

- Genetic & Genomic Analysis
- Diverse Urban & Pediatric Patient Populations
- High Through-Put Genotyping

UWSMPH

- Regenerative Medicine
- Statistical & Computational Analysis
- Super-Computing Capability

UW Milwaukee

- Urban & Environmental Health
- Community Engagement
- School of Nursing

Madison

Milwaukee

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Further Information

www.mfldclin.edu/pmrp

