I. PIONEERING

On September 19, 2002 Wisconsin Governor Scott McCallum joined the leadership of Marshfield Clinic and its Research Foundation (MCRF) in announcing the enrollment of the first of what would be 20,000 research subjects into the Clinic’s Personalized Medicine Research Project (PMRP). Governor McCallum stated in his remarks:

“Marshfield Clinic and its research division are dedicated to the public good, using science, scientific research, and scientific discovery to improve the quality of life in Wisconsin, throughout the nation, and really, throughout the world. I congratulate the people of north central Wisconsin for their understanding of the importance of research to our health and well-being, for their commitment to participation in research, and for the community spirit shown in efforts to promote health and the health of future generations.”

The President of Marshfield Clinic, Frederic Wesbrook, MD, summarized for the audience the objectives of the research project, which was supported by $2 million from the State government, $800,000 from the Federal government, and $1 million from Marshfield Clinic.

“This project seeks to accelerate the reality of personalized medicine, a concept that envisions an individually tailored approach to detecting, preventing, and treating disease based on a person’s specific genetic profile. Some day your doctor will have a set of genetic tests that will tell you personally what diseases you are at risk of getting, what you should do to prevent or delay those diseases, and what medicines you should take or not take.”

The start of PMRP enrollment was preceded by almost 2 years of planning. The Clinic’s potential to contribute to personalized medicine was first realized and the vision created...
by Michael Caldwell, MD, PhD, then the Director of MCRF and PMRP’s first principal investigator (PI). The grant proposals were prepared and the project organized by MCRF’s Associate Director, Steve Wesbrook, PhD. PMRP was executed beginning with enrollment by Catherine McCarty, PhD, MPH, then Director of the newly created Personalized Medicine Research Center and currently the project’s PI. The project’s inception, design, and implementation were guided by a steering committee of co-investigators that included, in addition to those mentioned above, the Clinic’s then Director of Clinical Research, Kurt Reed, MD; Director of Laboratory Medicine, Robert Carlson, MD; Director of Medical Genetics, David Schowalter, MD, PhD; Director of Corporate Communications, Donna Chapman-Stone (responsible for community and population information and education); and Clinic’s Chief Information Officer, Carl Christensen. The team received advice and counsel from an Ethics and Security Advisory Board (ESAB), which was led by Norman Fost, MD from the University of Wisconsin, and a Scientific Advisory Board (SAB), which was lead by David Altshuler, MD, PhD from Massachusetts’s Institute of Technology and Jurg Ott, PhD from the Rockefeller University.

Between a meeting of the ESAB in August 2001 and the first meeting of the SAB scheduled for September 13 and 14, the PMRP team was wrestling with a fundamental question raised by the ESAB. “Is the Marshfield Clinic Personalized Medicine Program [as it was then titled] a service program or a research program?” At the recommendation of the ESAB, the name would be changed and the focus narrowed, in large part out of the need to be clear to research study participants that they would not be receiving any personalized medicine services. Below is an unedited slide (Figure 1) that was sketched by the Associate Director of MCRF to guide the discussion of this question at a meeting of the steering group on Monday, September 10, 2001.

**Figure 1. Outline of Personalized Medicine**

Sep 10, 2001

**Personalized Medicine**

- as a field

**Service**

- [better healthcare]

**Consulting Services**

- Medical Genetics
- Pharmacogenetics

**Education**

- Provider
- Public

**Laboratory**

**Clinical Research**

**Basic Research**

**PERSONALIZED MED RESEARCH PROJECT**

- Individual Studies
- Multiple labs

- Research database
- Related studies
This working slide still remains a reasonable outline of the dimensions of personalized medicine. But what was perhaps most prescient about it was the recognition that even though the boundaries of PMRP would be narrowed to research, 1) the research project would serve as a catalyst for implementation of personalized medicine throughout the Clinic and 2) would create new linkages between scientific investigators and clinicians. What no one could predict, of course, was how much the United States would be changed by the events of the next day.

For the October 5-7, 2008 personalized health care (PHC) Summit in Utah, Marshfield Clinic was asked to focus on “how a community-based healthcare system has brought the key elements of PHC together to deliver more effective health care.” In doing so, we will address three elements of PHC: biomedical informatics; clinical care, including medical genetics and laboratory medicine; and medical research. The final section will provide some insights from our limited perspective that may have general import on future change and also address four of the major initiatives that are defining the PHC way ahead at Marshfield Clinic.

II. BIOMEDICAL INFORMATICS
In 1964 a group of physicians at Marshfield Clinic determined that the future of high quality health care would depend on computers. The Clinic has held to that vision for the past four decades and, as a result, developed one of the largest regional integrated health care information systems in the nation. The system spans most of the northern half of Wisconsin and is used by over 12,000 users, not only Marshfield Clinic employees, but also affiliated hospitals and treatment centers, and even competing physician group practices. The information network maintained by Marshfield Clinic has been structured in parallel to the health care delivery process and is of strategic importance in an effort to provide consistent, quality health care to a large geographical area. Marshfield’s ability to develop information systems has provided the needed flexibility to react to evolving clinical needs in a rapid manner and has assisted in point-of-care decision support for PHC.

Where We Are Today. Effectively delivering PHC requires many different systems working in concert at Marshfield Clinic. These include:

- Regional, integrated electronic health record (EHR)
- Semantic interoperability
- Clinical data warehouse
- Decision support
- An Internet-based portal that enables patients to directly interact with the Clinic’s information systems
- Tablet computers
- Population-based tools

Leveraging Clinical Information Systems to Support PHC Research. Marshfield Clinic believes that PHC is a process of continually improving knowledge and care, not a single endpoint. To that end, Marshfield has a history of integrating clinical computing with research computing.

- Population-based research. Marshfield Epidemiological Study Area (MESA) is a geographic population cohort in a 24 ZIP code area. The MESA database tracks a
subject’s geographical location since 1991 and has the ability to link subjects to
data stored within the Clinic’s data warehouse.

- Development of the Personalized Medicine Research Database (PMRD). PMRP leveraged existing Marshfield Clinic practice management and laboratory systems to recruit and collect genetic specimens. A cryptographic key system was developed to allow genotypic and clinical data to be combined for research studies, while protecting the privacy of research subjects. PMRD was created to store specimen sample identification numbers and the corresponding subject identification information. Later, PMRD was modified to accept validated genotype and phenotype data from the data warehouse.

- Phenotyping efforts. One essential requirement in assessing genetic impact on health and disease is the ability to characterize reliable phenotypes. Strong informatics and data management techniques, clinical guidance, statistical expertise, and clear communication with the disease experts enhance the ability to generate thoughtful and accurate phenotypes.

- Data mining. MCRF has entered into several collaborative data mining ventures with scientists from the University of Wisconsin-Madison to analyze large complicated genetic and phenotypic databases and develop algorithms that can predict patient reactions and outcomes to treatment.

- Episode-of-care. System monitors events in the EHR for patients who require special handling.

**Challenges and Future Directions in Biomedical Informatics.** The most important lesson we have learned is that systems to support PHC are not something that can be purchased “out-of-the-box” or simply “bolted-on” to existing systems and processes. They require commitment that spans years or decades. Achieving PHC requires a commitment to change, not only computer systems, but also health care processes. This implies that practicing clinicians must be involved at all stages of the development and implementation lifecycle. Another lesson is that the necessary integration cannot be achieved by silos, each focusing only on its own needs. Managers of clinical systems must believe that research is of value to the entire organization. Similarly, researchers must take the time to understand the ever-increasing demands on health care providers. It is acutely obvious to everyone at Marshfield Clinic that converting health care records to electronic form and eliminating paper charts (something that took 40 years to achieve) is only the first step toward a health care computational infrastructure that truly enables the vision of PHC. Marshfield Clinic is actively engaged in many projects to keep working toward the vision.

- Anonymized research data warehouse. The objective of this project is to develop a data warehouse that contains genetic, environmental, and clinical data.

- Natural Language Processing (NLP) of clinical documents. With over 55 million electronic documents containing health habits, family history, symptoms, environmental, and social factors, Marshfield Clinic is actively advanced in NLP to extract additional information for phenotyping and decision support.

- Phenotyping advances. Tools and techniques to improve the efficiency and interoperability of the phenotyping process are being developed.

- Pedigree mapping. Pedigrees add power to the genetic studies and allow rare disease studies to be conducted with limited cases.
• PHC reference library. The reference library will provide information on clinical, environmental, and genomic data and validated phenotypes.
• Research web portal. An Internet-based application (portal) that enables researchers to access genotype, clinical, and environmental information will be developed.
• Optimizing care through integration. Systematic workflow analysis and process mapping techniques are needed to seamlessly integrate not only the EHR, but also research innovations and discoveries into a busy practice setting.

III. CLINICAL CARE

Clinical Medical Genetics

Medical Genetic Services at Marshfield Clinic. The Medical Genetic Services Department at Marshfield Clinic provides clinical genetic consultation, diagnostic testing, and genetic counseling for patients and their families with genetic concerns. The greatest demand for clinical genetic services in adults is for single gene disorders including inherited cancers (BRCA1, BRCA2, HNPCC, FAP); connective tissue disorders such as Marfan syndrome, hemochromatosis, cardiomyopathy, Brugada, hemoglobinopathies, Huntington’s disease; and genetic susceptibility to adverse drug reactions. Annual unique patient referrals to Medical Genetic Services have grown from <30 in 1999 to over 300 in 2007.

The clinical genetics team realizes how important it is to raise awareness among patients regarding seeking genetic services, and has received grant support to increase the patient’s understanding about the value of genomic medicine. The initiative, led by Christina Zaleski, MS earned her the 2007 Leadership in Excellence Award for Community Service. The project involved creating multilingual (English, Spanish, Hmong) brochures and posters that discuss when and how to access genetic counseling for families with high-risk newborns or those who have experienced miscarriages, a stillbirth or other infant death. These materials were distributed to all birth centers in Wisconsin.

Utilization of genomic medicine to provide optimal clinic care requires that practitioners feel comfortable with ordering and interpreting genetic test results, as well as discussing these results with patients and their families. To help increase the awareness about medical genetics among primary care providers in Wisconsin and encourage practitioners to utilize clinical genetic services, Marshfield Clinic offers an annual state-wide conference entitled “Practical Genetics for Health Care Providers.”

The future of clinical medical genetics. With PHC emerging as an important contribution to clinical care, it is important to sustain and grow clinical genetics as a state-of-the-art service to both patients and healthcare professionals. The American Board of Medical Genetics is in the process of expanding the role of clinical geneticists and suggesting that geneticists broaden their services to liaison with other departments and be viewed as a resource for primary care patient management. It is also critical to attract students to consider careers in genetic counseling.

While genetic medicine has largely centered on provision of diagnoses and treatment for individuals with well-defined single gene disorders, genomic medicine when fully
realized will decipher genetic information derived from a person’s genome into predictors of disease susceptibility. A personalized medicine approach can be implemented for a particular individual and may consist, for example, of avoidance of certain disease risk factors or implementation of various screening modalities. Pharmacogenomic advances will facilitate testing for multiple genetically-mediated drug sensitivities, and genetic counseling will be needed for patients and their family members to understand the relationship between drug metabolism capacity and genetics that underlie them. Prospective genetic testing will be invaluable to the primary care provider in planning appropriate treatment.

To realize the promise of genomic medicine, health insurance barriers need to be overcome. Genetic referral and testing represents an exclusion in many insurance policies. Insurance denials entail additional workloads to genetics professionals, and in some instances appeals need to be made by the patient and not the healthcare provider. In order for patient care to be optimized there needs to be a three-way transfer of information between clinicians, researchers, and community members. PMRP has influenced interconnectedness between clinical care and research through its Community Advisory Group (CAG) and quarterly Personalized Medicine News (Figure 2). Accurate family histories from patients is challenging for many reasons. Bioinformatics approaches appear to have great promise.

**Figure 2. Personalized Medicine News**

**Laboratory Medicine**

Where we are today. Advances in genomics and related technology in the past decade have resulted in significant growth in molecular diagnostic testing and services, which has impacted almost all areas of laboratory medicine. Marshfield Laboratories was an early adopter of molecular diagnostics and has been performing such testing for over 12 years. As molecular testing increased in breadth and crossed into more traditional lab sections, it became apparent that for a regional laboratory, such as ours, to rapidly adopt this technology, a core laboratory with expertise in molecular testing was necessary. In 2005, Marshfield Laboratories formed its molecular pathology section to expand, coordinate, and standardize this growing area of testing services utilized for bacteriology, virology, coagulation, hematology, genetics, histology, and pathology. Prioritization of resources for development, validation, and implementation of new molecular testing is determined with input from clinicians and laboratory personnel representing all these areas. Test volumes in molecular pathology have grown faster than any other areas of the clinical lab during this time period (Figure 3).
The Molecular Pathology Laboratory is continuing to develop improved automation and expanding test menus. PHC tests in the area of oncology are increasingly prevalent, as these treatments are very expensive and carry high risks. Identification of KRAS gene mutations in codons 12 and 13 can predict whether or not an epidermal growth factor receptor (EGFR) inhibitor will be useful to treat colorectal cancer. A challenge for our laboratory to offer this testing is that the only commercially available testing product in the U.S. is labeled RUO (“for research use only”). Regardless of how well the test is validated, the use of RUO reagents in clinical testing significantly reduces or eliminates most forms of third party reimbursement. In the overall scheme of patient health care, it is clear that identifying patients who will not respond to costly treatments is prudent. However, KRAS mutation test reagents alone cost approximately $100/test. With little hope of reimbursement, the laboratory’s financial prospects of this testing are bleak. Our implementation of JAK2 testing to identify myeloid proliferative disorders, such as polycythemia vera, has been similarly hampered because the company holding exclusive intellectual property rights for clinical testing offers only RUO reagents for sale. These are not isolated instances.

**Figure 3. Test Volume Growth in Molecular Pathology**

Challenges and future directions in laboratory medicine. Biomarker discovery has proven to be much more difficult than initially envisioned. In addition, many new markers are part of a complex interaction with other genes and environmental influences making clinical utility difficult to ascertain. Also, while great strides have been made in the technology involved in DNA sequencing and genotyping, the availability of accurate phenotypes is lagging far behind. Another significant hindrance to bringing new molecular testing into the clinical laboratory is affordability, which is often linked to gene patents. Also, the complexity of patent and intellectual property regulations limits availability. The costs associated with advanced medical technology for PHC are disproportionately higher than traditional diagnostic services. If PHC is to grow,
healthcare institutions, Centers for Medicare and Medicaid Services, and insurance providers must recognize the overall healthcare savings of PHC and support testing through appropriate reimbursement.

IV. GENETIC RESEARCH

Personalized Medicine Research Project. PMRP was designed to support genomics research in three areas: pharmacogenetics, genetic basis of disease, and population genetics. The project required a concerted effort to develop not only genotyping and phenotyping capability and informatics infrastructure, but also needed to address issues such as logistics of population-based enrollment, bioethics, and stewardship of the biobank. From its inception, the project was intended to serve as a national resource for hypothesis generation and testing.

Nearly 20,000 adults have enrolled as of August 2008. Over 99% have consented to be re-contacted. In addition to the extensive EHR, the temporal span in years of clinical data available for PMRP subjects sets the cohort apart from other similar projects. The average span of clinical history for PMRP participants is 29+ years.

Pharmacogenetics. The study of the genetic impact on drug metabolism and disposition, and how this translates into drug efficacy or contributes to adverse drug events, has been a research priority at Marshfield Clinic. Below are ongoing extramurally-funded pharmacogenetics research studies.

- Efficacy and safety of statins
- Genetic impact on metformin metabolism and management of patients with type II diabetes
- Pharmacogenetics of tamoxifen response in treatment of breast cancer
- Pharmacogenetics underlying response to beta blockers in patients with glaucoma
- Pharmacogenetics of warfarin metabolism

Genetic Basis of Disease. Outlined below are ongoing extramurally-funded studies being conducted at Marshfield Clinic on the genetic basis of disease.

- Cataracts
- Scoliosis and other vertebral malformation
- Genetic and environmental interaction and risk factors contributing to multiple sclerosis
- Myocardial infarction risk and influence of genetic variation on chromosome 9p21

In addition, Marshfield Clinic investigators are conducting internally funded studies using the PMRP research infrastructure in hypertensive heart disease, Alzheimer’s disease, fibromyalgia syndrome, and osteoporosis.

V. THE WAY AHEAD

Marshfield Clinic is a robust, comprehensive and highly integrated health care system. It has over 750 physicians and 6,500 additional staff at 41 centers in a primary service area that includes 60% of Wisconsin geographically. Annually, the Clinic sees approximately 370,000 unique patients. In support of its mission to serve patients through accessible, high quality health care, research, and education, Marshfield Clinic supports strong
programs in research and graduate education, maintains its own 147,000 member HMO, and provides through its Community Health Center and other programs health care for people irrespective of their ability to pay. But the capability of even a large and progressive health care system to deliver PHC depends largely on external factors, including the general advancement of science, speed with which industry commercializes discoveries, intellectual property law, government and private medical insurance payment schedules, and many others.

To the degree to which Marshfield Clinic can control its own PHC future, it will continue to do what it has done well over the past decade. This includes striving for even better integration of medical research and clinical practice. Marshfield Clinic and MCRF are either leading or substantially contributing to a number of new initiatives that will also shape its way ahead.

**Clinical and Translational Science Awards (CTSA)**

University of Wisconsin School of Medicine and Public Health and MCRF partnered to receive a NIH Clinical and Translational Science Award in September 2007. Currently supporting a national consortium of 34 academic medical research institutions, plus partnering institutions, CTSA is scheduled to link 60 such institutions by the year 2012. The consortium has been designed to ensure broad access to CTSA resources, enhance communication, and encourage information sharing.

Marshfield Clinic also joined in the fall of 2007 with five academic health science schools/colleges at the UW-Madison to create the UW Institute for Clinical and Translational Research (ICTR). ICTR was established to “create an environment that transforms research into a continuum from investigation through discovery and to translation into real-life community practice, thereby linking even the most basic research to practical improvements in human health.”

**Wisconsin eHealth Care Quality and Patient Safety Initiative**

On November 2, 2005, Wisconsin Governor Jim Doyle came to Marshfield Clinic to sign Executive Order 129 creating the Wisconsin eHealth Care Quality and Patient Safety Board. Governor Doyle charged the Board with establishing an action plan for the statewide adoption of EHRs and the exchange of health care information by the year 2011 (http://ehealthboard.dhfs.wisconsin.gov/). Referring to the Clinic’s leading role in developing and using EHRs, its successful quality initiatives, and its history of championing for health care reform, he stated that “Marshfield Clinic is truly the place to make this announcement.”

Whereas progressive and committed organizations can do much on their own, no single institution has enough information on all their patients to provide optimal health care, and health information exchange cannot be done by a single institution. A statewide eHealth information infrastructure will improve the quality and cost of health care in Wisconsin by 1) ensuring health information is available at the point of care for all patients, 2) reducing medical errors and avoiding duplicative medical procedures, 3) improving coordination of care between hospitals, physicians, and other health professionals, 4) furthering health care research, and 5) providing consumers with their health information to encourage greater participation in their health care decisions. The goal is to achieve
100% electronic health data exchange between payers, health care providers, consumers of health care, researchers, and government agencies as appropriate.

**Personalized Health Care Testbed**
Achieving the computational infrastructure for PHC will require the integration of many different components. It will also require two very different types of research endeavors. The first type of endeavor will involve research groups that have deep expertise in one, or a few, of the components. These groups will develop new theories and approaches to specific problems in PHC. For example, one of these groups may develop improved knowledge discovery tools and a health care workflow engine. Essentially, these groups focus on one piece of the puzzle. The second type of endeavor will involve the development of a PHC Testbed (Figure 4). The number of potential PHC interventions is likely to increase exponentially in the coming years. The role of a PHC Testbed is to evaluate the impact of implementation of possible PHC interventions in real clinical practice, at a speed that is more rapid and at a cost that is much below what would be required by a de novo conventional clinical trial. Testbed institutions will need to have expertise across a broad range of domains.

**Figure 4. Personalized Health Care Testbed Architecture**

There are three foundation components in a PHC Testbed: large scale genotyping, population coverage, and longitudinal clinical data. Potential PHC interventions that will be evaluated by a PHC Testbed can be divided into major groups. The first are those that involve associations between genetic or metabolic markers that are measured by existing broad screening tools, such as large-scale SNP chips. The second base-level attribute of a PHC Testbed is population coverage. Having a large and stable population base allows prior information to be applied to future clinical care in a large percentage of cases. The third base level competency for a Testbed site is an extensive repository of longitudinal clinical data. Since the future of PHC is certain to include lifetime EHRs, attempting to evaluate PHC interventions without many years of prior clinical data can yield spurious results.

The next level in the PHC Testbed is semantic interoperability. Without a consistent framework for what individual clinical terms and concepts mean, it will be impossible to reliably identify patients or evaluate outcomes. Above the semantic layer is the knowledge layer, which includes two components, analytics and knowledge discovery and knowledge assimilation. The process of defining clinical phenotypes and clinical outcomes involves the use of knowledge discovery techniques. Any successful PHC
Testbed must have an active knowledge discovery group that can rapidly address new questions. Knowledge assimilation is the process of incorporating structured knowledge from outside an organization into the computational knowledge framework of the institution. Any PHC Testbed will need a structured approach to knowledge assimilation so that new PHC intervention can be incorporated efficiently into the institution’s knowledge base.

Clinical care involves complex processes with multiple steps. Simple rule-based systems are inadequate to capture these clinical workflows. The implementation of PHC will require the implementation of electronic workflows that support the complex, multi-actor nature of clinical care. The ultimate goal of PHC-driven electronic workflows is to improve clinical outcomes. PHC Testbeds will need both experience evaluating clinical outcomes and access to comprehensive data in order to determine true outcomes. This is much easier in sites with stable patient populations and broad population coverage. Two other components of the PHC Testbed span all levels: ethics and security and standards.

For PHC interventions to become mainstream therapy, they will need to be evaluated not only in highly controlled studies but also in a real world practice setting, like those represented by a PHC Testbed. A successful PHC Testbed will require expertise in such a broad range of domains. Many institutions have strengths in one, or a few areas, but very few have strength across the entire spectrum required for a PHC Testbed. However, the success of PHC will be markedly delayed if such PHC Testbeds are not available. Marshfield Clinic represents a unique combination of capabilities across this spectrum.

**Wisconsin Genomics Initiative (WGI)**

On October 10, 2008 Wisconsin Governor Jim Doyle announced the Wisconsin Genomics Initiative, which is a collaborative research effort among Marshfield Clinic, Medical College of Wisconsin, University of Wisconsin School of Medicine and Public Health, and University of Wisconsin–Milwaukee. He stated that “By capitalizing on the unique strengths of each institution, we have a rare opportunity to meet an important scientific and public health need that could otherwise not be met.” The vision of WGI is to be able to predict for individual patients in a clinical setting the risks of disease susceptibility and treatment response using the combined power of cutting edge genetic, phenotypic, and environmental analyses, thereby making the promise of personalized medicine a reality (Figure 5).
The key elements of its phase I WGI strategy are to 1) genotype up to 20,000 PMRP participants for 1,000,000 genetic markers, 2) validate selected target phenotypes and multiple clinical attributes from the Marshfield Clinic EHR for the PMRP cohort, 3) integrate genetic, phenotypic, and environmental information databases and develop the search engines to use data efficiently for scientific discovery, and 4) to build predictive computational models using machine learning and super-computer capability, for the key equation, Genetic + (Environment and Clinical) = Phenotype. It will then conduct initial predictive studies (diabetes, obesity, coronary artery disease, and atrial fibrillation) to test and improve the scientific platform, as well as a genome-wide association study (GWAS). WGI institutions anticipate making the WGI scientific platform, information, and methods available to scientists across the country. In phase II, WGI plans to add a 20,000-person urban cohort, a pediatric cohort, and to expand substantially predictive studies.