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# Marshfield Clinic Personalized Medicine Research Project (PMRP): design, methods and recruitment for a large population-based biobank

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**Objectives:** The objective of this paper is to summarize the planning for Phase I of the Marshfield Clinic Personalized Medicine Research Project (PMRP) and to describe the recruitment efforts in the first 2 years. **Methods:** The purpose of Phase I of the PMRP was to develop a large population-based biobank with DNA, plasma and serum samples to facilitate genomics research. Planning and consultation was facilitated with three external boards: the Ethics and Security Advisory Board; the Scientific Advisory Board; and the Community Advisory Group. Commencing in September 2002, residents aged 18 and above who resided in 1 of 19 zip codes surrounding Marshfield, WI, USA, were invited to participate. After providing written informed consent, participants completed brief questionnaires that included questions about demographics, some environmental exposures, family history of disease, and adverse drug reactions, as well as family members living in the study area. Participants provided 50 ml of blood from which DNA was extracted and plasma and serum samples were stored. The informed consent document allowed access to electronic medical records and included language about non-disclosure of personal research results. A tick-off box was also included so that participants could either allow or decline subsequent recontact for future research studies. **Results:** A total of 17,463 subjects were enrolled during the first 23 months of recruitment (44.3% of the residents who the Research Project Assistants were able to contact). The participants ranged in age from 18 to 98.5 years (mean = 48.9, median = 48); 57.2% (n = 9986) were female. Self-reported race in the study cohort was similar to the year 2000 census for Wood County, WI, USA, with the majority (98%) reporting themselves to be White Caucasian. The majority of subjects (n = 13,391, 76.7%) indicated that they had German ancestry. Only 142 participants (< 1%) opted out on the consent form for contact for future studies. The majority of the cohort reported that their current area of residence was a suburb, city or village (n = 10630, 60.87%); the remainder reported residence in a rural home or hobby farm (n = 5365, 30.72%), or a working farm or ranch (n = 1451, 8.31%). More than half the cohort (n = 9409, 53.88%) had lived on a working farm at some point in their life. **Conclusion:** The PMRP database will allow research in three areas: genetic epidemiology, pharmacogenetics, and population genetics. The size and the stability of the population as well as the relative ethnic homogeneity will help facilitate longitudinal studies with valid research results that are not biased by population stratification.

April 2003 marked the 50th anniversary of the discovery of the molecular structure of DNA [1], as well as the completion of the Human Genome Project, the publicly funded international research effort to sequence the entire human genome [101]. With the completion of the Human Genome Project 2 years ahead of schedule, Dr Francis S Collins and his colleagues at the National Human Genome Research Institute, NIH, published their vision for the future of genomics research [2]. Their Grand Challenge II-1 is to 'develop robust strategies for identifying the genetic contributions to disease and drug response' [2] and they mention the Marshfield

Clinic Personalized Medicine Research Project (PMRP) as one of several population-based cohort studies that will be positioned to meet this goal.

It has been suggested that common gene variants are responsible for the majority of common diseases [3,4], and population-based study designs may be useful to help identify these common variants and their relative importance in the population. Some scientists have advocated for larger sample sizes to increase statistical power to detect disease genes [5] and some have argued for a larger number of SNPs, especially for people of African descent [6]. Recent reviews of the results

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of genetic association studies have revealed very poor reliability and validity of published data, often due to study bias, insufficient sample size, and population stratification [7–9]. Researchers have advocated for larger sample sizes in ethnically homogeneous populations to increase the validity of genetic studies [10]. Replication of study results in other populations has also been stressed, necessitating large, well-characterized study cohorts that could be used for validation.

In addition to the ongoing debate about the most appropriate study design and number of SNPs to identify disease genes in population-based association studies, there has been a continuing debate surrounding the ethical and informed consent issues involved with the creation of DNA banks [11–20], the acceptability of this type of research to the general public [20–22], and the concept of shared benefit with study participants [23].

The PMRP is a population-based cohort study with stored DNA, plasma and serum. It also has access to a comprehensive electronic medical record. The database will allow scientists to conduct research in the areas of genetic basis of disease, pharmacogenetics, and population genetics. Many of the ethical, legal, social and scientific issues encountered during this project have been resolved with the assistance of external advisory boards, and some issues will continue to evolve. The purpose of this paper is to describe the design and methods of the project, as well as the recruitment results from the first 2 years.

### Methods

The PMRP was designed in three phases:

- study planning, consultation, and initial recruitment
- establishment of the infrastructure and construction of the PMRP database to allow it to be a national resource, and expanding the database
- genetic discovery projects and physician and community education.

The following sections describe the methods for the Phase I stage of the project.

#### *Ethics and Security Advisory Board*

The Ethics and Security Advisory Board (ESAB) met twice prior to the initial subject recruitment to discuss and provide advice on many issues, including:

- anonymity
- consent

- publication
- disclosure of results
- recontact of participants
- involvement of the public
- relationship of the ESAB to the Marshfield Clinic Institutional Review Board (IRB)
- distribution of benefits
- access to the database
- inclusion of minors

The outcome of many of these discussions is evident in the consent form (see Appendix I). The decision not to enroll minors was made for largely scientific reasons, because the ESAB felt that the data security that would be established made the project one of low risk to subjects and, therefore, not an ethical problem. Scientifically, a cohort study is not the most efficient study design for diseases in children because most genetic diseases of childhood are relatively rare.

The Marshfield Clinic received a Certificate of Confidentiality from the National Institutes of Health (NIH) protecting the PMRP research database from forced disclosure, even under court order. The IRB of Marshfield Clinic approved all forms and procedures for the PMRP.

#### *Community consultation*

Community consultation involved three major activities:

- focus group discussions prior to and during the enrollment period
- public education through media releases, community talks, a website, and video
- organization of a Community Advisory Group (CAG) prior to and during enrollment

Three series of focus group discussions were held during the planning phases of the project to determine levels of understanding as well as general attitudes and concerns about genetic research among community residents, including Marshfield Clinic employees. All focus group discussions were conducted and interpreted by an independent market research firm.

Separate IRB approval was obtained 6 months after initiating recruitment to invite people who said that they were 'not interested' in participating in the PMRP to attend focus group discussions to further explore their reasons for refusal. These focus group discussions were held in July and August 2003, 10 months after enrollment commenced, and were also conducted and analyzed by the same independent market research firm. Four focus groups were held; three from

different communities after primary enrollment had been completed, and one with staff and spouses of Marshfield Clinic employees.

The website for the PMRP was developed and is accessible through the Marshfield Clinic Research Foundation website [102]. The site has information about the PMRP, including an overview of the program, detailed programmatic materials, links to informative websites, and updates on program progress, emerging discoveries, and planned studies. A full-color flyer was developed with the guidance of the CAG (see Appendix II). It highlights the key points of the project, has a photo and quote from one of the members of the CAG, and includes contact details. The flyer is displayed throughout the Marshfield Clinic and in local businesses. It was included in the daily *Marshfield News Herald* on a monthly basis during peak recruitment efforts and was added as an insert with the initial invitation letter to potential participants at the suggestion of the CAG. A 15-min video was developed and played throughout the Clinic and played for community group presentations.

### *Community Advisory Group*

The CAG is comprised of 15 members who represent various demographics within the target population (age, gender, ethnicity, and geography). Representation was also specifically sought from the following segments of the community: economic (business, industry, agriculture, employers, and workers), education (teachers, administrators, and parents of students), health (public and private), faith-based, religious, media and public officials (elected and/or appointed, local and state level), previous Marshfield Clinic research participants, civic organizations, and community foundations. The group met twice prior to initial enrollment and was reconvened twice during the first 12 months of enrollment. CAG members were asked to provide advice and assistance in the following areas: reaction and options on the understanding of the PMRP by the community; how to interact with the community about the PMRP; identification of potential problems and recommendations for solutions; sensitivities, needs and desires of various ethnic groups; effectiveness of messages, promotional and other PMRP materials; suggestions on other groups in the community to talk to or involve; and how to develop a process for community benefit sharing as a result of the PMRP. The CAG also served as a community liaison in support of the PMRP.

### *Scientific Advisory Board*

A Scientific Advisory Board (SAB) was assembled to provide guidance on scientific issues. The SAB includes members with expertise in computational biology, pharmacogenetics, statistical genetics, and molecular epidemiology. The group met twice prior to patient enrollment and reconvened 1 year after initiation of enrollment. Some of the issues discussed included genotyping strategies, haplotyping, development of cell lines versus whole genome amplification, suggestions for collaboration, suggestions for how to create a national user center, processes to access DNA samples and phenotypic data, and funding. SAB members also provided advice on proposed internal studies using the PMRP database. An internal scientific planning group, comprised of Marshfield Clinic clinicians and scientists from various disciplines, met monthly to discuss various scientific issues and research opportunities.

### *Recruitment and enrollment*

Participant enrollment commenced on September 18, 2002. The PMRP was officially launched with an on-site press conference that featured Wisconsin Governor Scott McCallum. Initial recruitment was targeted to people aged 18 and older who currently reside in 1 of 19 zip codes around Marshfield, WI, USA, and for whom at least one member on their Marshfield Clinic account had received care at the Marshfield Clinic in the previous 3 years. The 19-zip code area selected is known as the Marshfield Epidemiologic Study Area (MESA) [24].

The Marshfield Clinic is an integrated regional healthcare system with 700 physicians in 41 locations throughout central and northern Wisconsin. All major medical specialties and subspecialties, except whole organ transplant, are covered within the Clinic system. Except for the city of Marshfield, MESA residents reside rurally or in small towns or villages. The annual in- and out-migration is very low, making it ideal for prospective studies. By sharing an electronic medical record with neighboring hospitals, inpatient diagnoses, out-patient diagnoses and procedures are captured for MESA residents. Many MESA residents are also members of the Marshfield-Clinic-sponsored health maintenance organization, the Security Health Plan, allowing capture of health events that may occur outside the Marshfield Clinic system of care.

Following the initial awareness activities that included community talks and media releases, an information/invitation letter was sent to all

eligible residents in the Clinic system. This letter introduced the program and included a brief one-page informational brochure to provide an overview of PMRP. The letter included a toll-free number for inquiries, and a website address for further information about the project. Residents were alerted to expect a follow-up telephone call from a Research Project Assistant within 2 weeks to describe the project in more detail and invite participation, and schedule an appointment time if interested. Within a week of the mailing, Research Project Assistants placed telephone calls to gauge the level of interest of each eligible household member and made appointments with individuals who indicated interest in enrollment. Seven call attempts were made to contact an individual. Messages were left after the first, third and sixth call. If not successful by the seventh call, the subject became ineligible for reason of non-contact. The baseline questionnaire (Appendix III) and informed consent documents (Appendix I) were mailed along with the appointment reminder. Interested participants reporting to the PMRP reception center were greeted by a Research Project Assistant who ascertained their level of knowledge and interest in enrollment. After review of the consent document, written informed consent was obtained. Subjects were asked to complete the questionnaire designed to collect familial and some environmental data (current occupation and industry, smoking, and alcohol intake), if not completed prior to their appointment. Questionnaires were reviewed by a Research Project Assistant to check for completeness and confirm accuracy of the information provided by the subject. The Research Project Assistant measured and recorded height to the nearest half inch and weight to the nearest half pound. A trained phlebotomist drew 50 ml of blood. The enrollment procedures required approximately 30 min. Participants received US\$20 to cover their travel expenses and time.

### *DNA extraction*

The Gentra's AUTOPURE LS<sup>®</sup> system is used for the extraction of DNA from 30 ml of blood from each patient. The DNA extraction process is fully automated and is based on the procedure of Ciulla *et al.* [25]. Briefly, the buffy coats containing the white blood cells from three 10-ml samples of blood are mixed with 30 ml of red blood cell lysis solution in a 50-ml tube. The tube is then incubated at room temperature for 5 min, inverted several times and spun at 2000 rpm for

2 min. Following centrifugation, the supernatant is decanted and the white blood cell pellet is resuspended in 3.3 ml of protein precipitation solution. A total of 10 ml of cell lysis solution is added to the center of the sample, the tube is vortexed for 10 s and then centrifuged at 2000 rpm for 6 min. The supernatant is transferred into a clean 50-ml centrifuge tube containing 10 ml of 100% isopropanol, inverted several times and then centrifuged at 2000 rpm for 2 min. The supernatant is removed, the DNA pellet is washed in 70% ethanol, and the tube is centrifuged at 2000 rpm for 1 min. Ethanol is then carefully removed from the tube and the DNA is resuspended in 3 ml of DNA hydration solution for 72 h. Finally, the DNA is quantitated and stored permanently at -80°C. After isolation, the DNA samples are coded and a map of the samples in each freezer is maintained to allow easy retrieval for future genotyping. Plasma and serum samples are also stored for each study participant.

### *Data management*

The questionnaires are scanned and the data are entered into a secure database for management. The scanned images of the questionnaires and consent forms are stored electronically for subsequent retrieval if necessary. Comparisons of demographic data were made with the 2000 US Census for Wood County, WI, USA [26]. SAS was used for analyses and a  $p < 0.01$  was considered statistically significant due to the large sample size. Participants were defined as residents who signed informed consent documents and provided a blood sample. Non-participants were defined in two different ways for comparison with participants:

- residents who received letters and for whom we were able to make contact and they explicitly said 'no'
- all residents who received a letter of invitation (unless the letter was returned due to having moved with no forwarding address, and the individual was known to be alive)

Any known deaths were removed from the denominator.

### *Future studies*

Traditional family-based linkage analyses will be possible with the PMRP cohort, as well as population-based association studies. The population-based association studies will allow researchers to use traditional epidemiologic tools, such as logistic regression, to model the independent effects

of environmental and genetics factors (as well as their interaction) on the development of disease and differential response to medications. De-identified data sets will be created for analyses. All data are coded, rather than anonymized, to allow the incorporation of additional phenotypic, environmental and genetic data to the de-identified analysis database in the future.

### Results

#### *Focus group discussions*

Four initial focus group discussions were held: two in the MESA central area (the zip codes surrounding Marshfield) and two in MESA north (a 10-zip code region in northern Wisconsin). Three of the groups were made up of eight adults; one had nine adults. There were 17 males and 16 females in the four groups, aged 18–78 years. Employees of the Marshfield Clinic were not eligible for these discussions. The majority of the participants (27 of 33) said that they would be interested in participating in the PMRP, but that their participation would be conditional upon trusting that confidentiality would be maintained regarding their DNA and medical records. Primary hypothetical reasons cited for not participating in the PMRP were:

- lack of interest
- lack of time to consider and participate in the project
- lack of personal benefit

The primary source of information about genetic research for the focus group participants was the mass media, especially television. They also suggested direct contact with potential PMRP participants to inform them about the project. All groups recommended that the enrollment visits be limited to a maximum of 30 min and that a monetary incentive (US\$25–50) be offered to offset travel costs and time away from work.

The second series of focus groups was used to gather information about how best to include Marshfield Clinic staff participation in the PMRP. Four focus groups comprised of employees who do and do not require medical training for their jobs, not including physicians and nurses, were conducted in October 2001. More females than males participated (36 versus 10). These staff focus group participants indicated that the three most important factors that would affect their decision to participate in the PMRP would be:

- their trust in the security and privacy policies of the Research Foundation

- the effectiveness of the communication about the program
- the convenience of the enrollment process

Two focus groups were held with Marshfield Clinic patients to review written documents (two letters of invitation, a brochure explaining PMRP, the consent form, 'Frequently Asked Questions' and the baseline questionnaire) for the PMRP. The two focus groups were made up of 9 males and 12 females aged 20–80 years. Agreement was nearly unanimous that the consent form be sent to people who had already agreed to participate. Although the majority of focus group participants said that they would be interested in participating after reading the materials, only half indicated that they would take action to sign up for the study (i.e., they would need personal contact to organize an appointment time). After reading the documents, answers to three questions remained unclear to many participants:

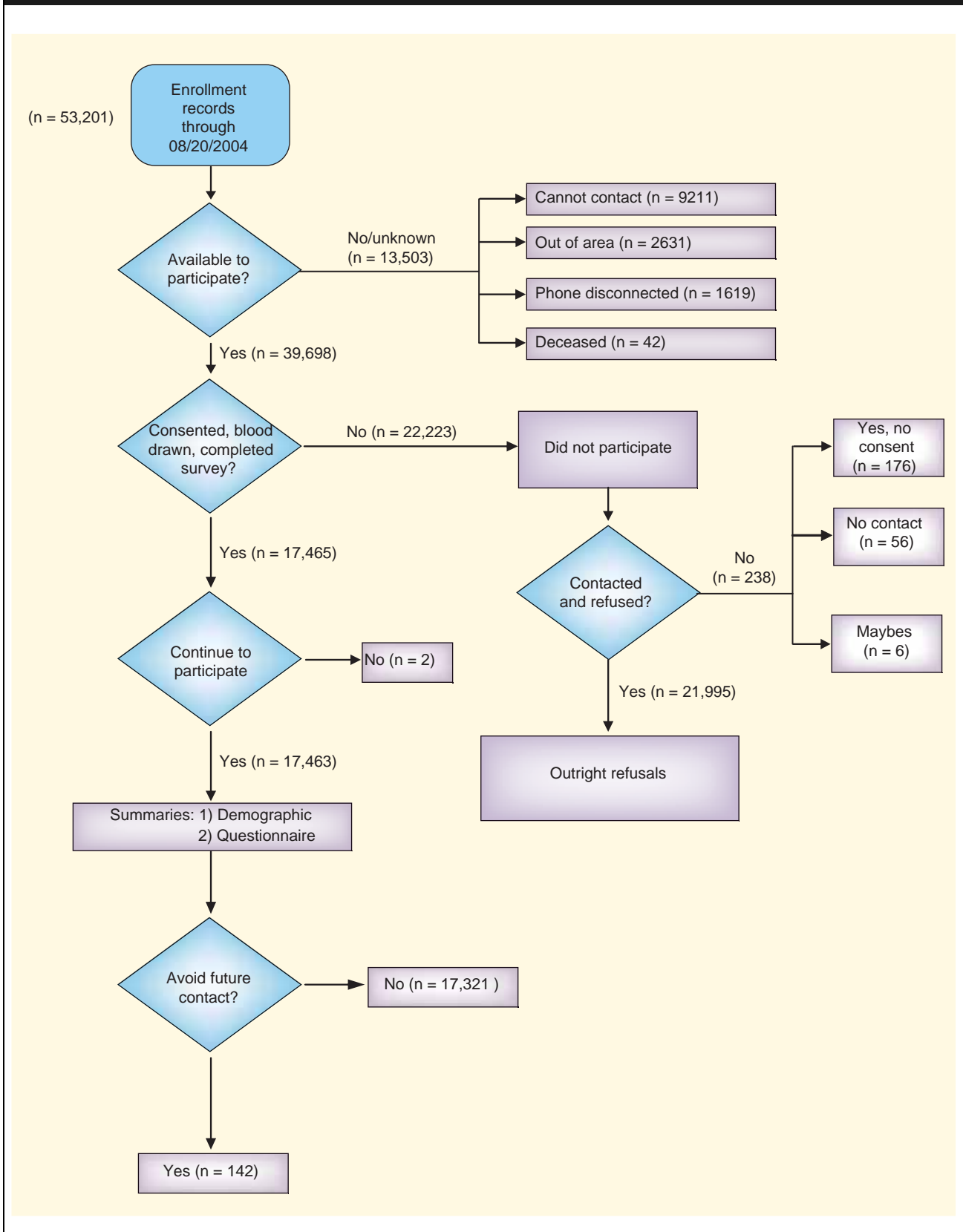
- the degree of confidentiality risk
- lack of clarity regarding the reasons that they would not get personal health information returned to them as a result of study participation
- details regarding process involved with participation

Written materials were revised in response to the focus group feedback.

The final series of four focus group discussions were held 10 months after commencing recruitment with residents who did not participate in the PMRP. The ages of the 44 participants ranged from 18 to 69 years and 21 (47.7%) were male. Approximately half of the participants indicated that the perceived time commitment to learn about and enroll in the project was the main reason that they chose not to participate. They perceived that there was little or no benefit for them in relation to the time it would require to participate, especially for residents living outside of Marshfield. A total of 30 of the 32 community members had little or no awareness of the PMRP and recommended further community awareness activities. Focus group participants also recommended that the written information be more concise. Suggestions made by the focus group participants for strategies to maximize enrollment included the following:

- rewrite the first paragraph of the introductory letter to simplify the language (subsequently done)

Figure 1. Summary of enrollment during the first 2 years of recruitment for the Personalized Medicine Research Project.



**Table 1. Age- and gender-specific mean (median) number of unique diagnoses for calendar year 2003 in participants and non-participants of the PMRP.**

Age	Gender	Participation status		
		Mean diagnoses (median)		
		Participants	Eligible, but could not be reached	Outright refusals
18–64	Female	13.30 (11)	11.14 (9)	10.98 (9)
	Male	9.51 (7)	7.41 (5)	7.27 (5)
65–75	Female	19.92 (18)	16.89 (15)	16.76 (15)
	Male	17.90 (15)	16.15 (13)	15.76 (13)
≥ 76	Female	23.54 (21)	21.72 (19)	21.16 (18)
	Male	22.52 (19)	21.87 (18)	21.53 (17)

PMRP: Personalized Medicine Research Project.

- include only the ‘Frequently Asked Questions’ and flyer along with the introductory letter (subsequently done)
- increase awareness of the PMRP through media
- enroll at other sites (a site in a local town was organized on a weekend)
- develop a newsletter to send to all participants to encourage them to refer friends and relatives to the project
- consider a wind-up campaign creating a deadline for enrollment
- 2.43% blood draw
- 2.05% privacy
- 1.07% unspecified
- 0.98% oppose genetic test
- 0.04% religious

*Participation*

Enrollment for the first 23 months of the PMRP is summarized in Figure 1. A total of 17,463 subjects were enrolled during that time period (44.3% of residents whom Research Project Assistants were able to contact). The participants’ ages ranged from 18 to 98.5 years (mean = 48.9, median = 48); 57.2% (n = 9986) were female. There was a lower percentage of females in the non-participant groups (49.38% for the 22,233 people whom we were never able to contact, and 49.34% for the 21,995 residents who were contacted but refused to participate). The mean age in these two non-participant groups was the same as for the participants. A comparison of participants and non-participants revealed that participants had a higher mean number of unique diagnoses within the Marshfield Clinic system than residents who refused outright to participate or residents whom staff were unable to contact after a minimum of seven telephone calls (Table 1). At all ages, women in all three groups had a greater number of mean diagnoses than men. The reasons given for refusal to participate included:

- 71.33% not interested
- 16.44% inconvenience
- 5.66% other

The age distribution of PMRP participants was similar to the Wood County Census for the year 2000 (Table 2). Self-reported race in the study cohort was also similar to the year 2000 Census for Wood County with the majority (98%) reporting themselves to be White Caucasian (Table 3). The majority of subjects (n = 13,391, 76.7%) indicated that they had German ancestry (Table 4). Only 142 participants (0.81%) opted out on the consent form for contact for future studies. Approximately 10% of study participants elected to donate the US\$20 reimbursement back to the PMRP or other medical research.

Despite the fact that enrollment was organized at Marshfield Clinic regional centers so that subjects would not have to travel great distances, participation was inversely correlated with the number of miles away from Marshfield (Figure 2, R<sup>2</sup> = 0.3887). Distance from Marshfield ranged from 0 to 46.4 miles and the participation rates ranged from 31 to 54% for the 19 individual communities.

The majority of the cohort reported that their current area of residence was a suburb, city or village (n = 10,630, 60.87%), while 30.72% (n = 5365) lived in a rural home or hobby farm and 8.31% (n = 1451) lived on a working farm or ranch. More than half the cohort (n = 9409, 53.88%) reported that they had lived on a working farm at some point during their life.

The majority of the cohort (n = 14,247, 81.58%) indicated that they were currently employed full-time for wages. The most common business in which subjects were employed

**Table 2. Age distribution of PMRP participants and comparison with the 2000 Census estimates for Wood County, WI, USA.**

Age category	PMRP participants	Year 2000 Census estimates
18–20	844 (4.83%)	2820 (5.02%)
21–24	1026 (5.88%)	3005 (5.35%)
25–34	2158 (12.36%)	9026 (16.07%)
35–44	3204 (18.35%)	12,425 (22.12%)
45–54	3550 (20.33%)	10,415 (18.54%)
55–59	1499 (8.58%)	3681 (6.55%)
60–64	1208 (6.92%)	3202 (5.70%)
65–74	2102 (12.04%)	5522 (9.83%)
75–84	1509 (8.64%)	4324 (7.70%)
≥ 85	363 (2.08%)	1750 (3.12%)
Total	14,803 (100%)	56,170 (100%)

PMRP: Personalized Medicine Research Project.

**Table 3. Self-reported race of PMRP participants (n = 17,463) and comparison with year 2000 Census estimates for Wood County, WI, USA.**

Race category	PMRP participants	Wood County, year 2000
White Caucasian	17,187 (98.4%)	72,625 (95.4%)
Hispanic/Latino/Spanish	175 (1.0%)	709 (0.9%)
American-Indian	137 (0.8%)	775 (1.0%)
Asian/Hmong	67 (0.4%)	1313 (1.7%)
Other	38 (0.2%)	347 (0.5%)
Black/African-American	29 (0.2%)	326 (0.4%)

PMRP: Personalized Medicine Research Project.

**Table 4. Self-reported ancestry/ethnic origin of PMRP participants (n = 17,463).**

Ancestry/ethnic origin	Number (percent)
German	13,391 (76.7%)
Irish	2888 (16.5%)
English	2807 (16.1%)
Other	2712 (15.5%)
Polish	2149 (12.3%)
Norwegian	2044 (11.7%)
French/French Canadian	1672 (9.6%)
Swedish	1136 (6.5%)
Dutch	1073 (6.1%)
Czech	651 (3.7%)

PMRP: Personalized Medicine Research Project.

in the previous 5 years was educational, health and social services (21.31%), followed by manufacturing (13.44%), and then agriculture, forestry, fishing, and hunting (11.3%) (Table 5).

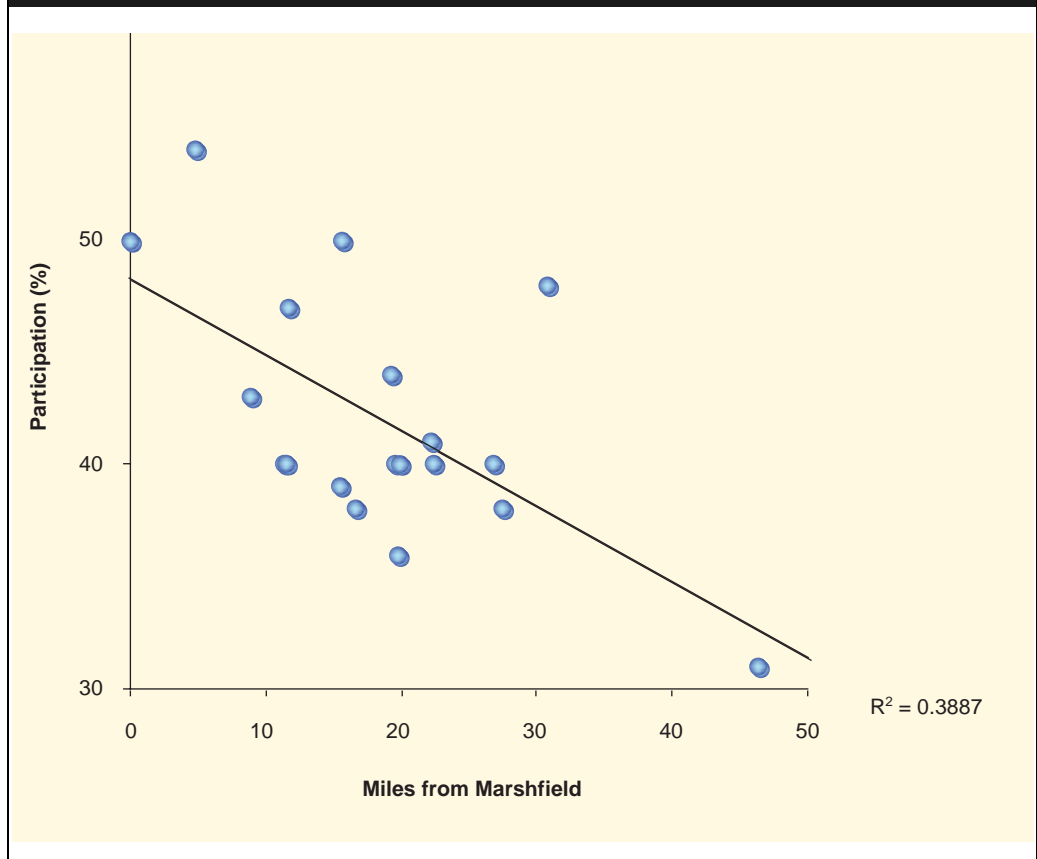
Of the subjects, 18% (n = 3195) were current smokers, while 27.98% (n = 4887) were past smokers, and 53.58% (n = 9356) had never smoked.

#### Discussion

Researchers at the Marshfield Clinic have taken great care to design and undertake the PMRP, in hopes of developing a resource that will serve the larger research community and address the Grand Challenge issued by Dr Francis S Collins and his colleagues at the National Human



**Figure 2. Relation of participation rate to miles from Marshfield in the 19 selected communities.**



**Table 5. Self-reported current business or industry for the past 5 years in the PMRP participants.**

Business/industry	Number (percent)
Services: educational, health, and social	3786 (21.31%)
Manufacturing	2389 (13.44%)
Agricultural, forestry, fishing, and hunting	2008 (11.30%)
Retail trade	1713 (9.64%)
Services: professional, scientific, management, and administrative	1568 (8.82%)
Services: arts, entertainment, recreation, accommodations, and food	1391 (7.83%)
Construction	1260 (7.09%)
Services: other (except public administration)	1022 (5.75%)
Transportation and warehousing	886 (4.99%)
Finance, insurance, real estate, and rental and leasing	628 (3.53%)
Information and communication	421 (2.37%)
Wholesale trade	247 (1.39%)
Utilities	132 (0.74%)
Public administration	129 (0.73%)
Services: waste management	97 (0.55%)
Active military duty	67 (0.38%)
Mining	25 (0.14%)

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Genome Research Institute [2]. The robust enrollment (nearly 18,000 participants) and success to date reflect the guidance and oversight provided by community leaders as well as experts in the fields of bioethics, genetic epidemiology and pharmacogenetics.

There are many advantages to the PMRP. First, the population of central Wisconsin is fairly stable, with a relatively low annual in- and out-migration. Along with written informed consent that allows continued access to electronic medical records and recontact where

consent was given to allow the collection of additional phenotypic or environmental information, this stable population will help to facilitate longitudinal genetic and epidemiologic studies. Second, the relative ethnic homogeneity of the study population should help researchers to avoid population stratification in their analyses, which has been suggested as the major cause of low reproducibility of genetic association studies in the past [4]. To some researchers, the ethnic homogeneity might be considered a disadvantage due to the limited generalizability of study results. However, we feel that the ethnic homogeneity represents an advantage for analytical reasons. The size of the study population and slight bias toward increased participation by people with more medical diagnoses are also advantages for studying many diseases. Nonetheless, the current cohort size of approximately 18,000 adults may be insufficient for studying rare diseases. This problem can be overcome by recruiting people with certain diseases and selecting appropriate population-based controls from the PMRP cohort.

The response rate to the PMRP was relatively high considering that participants were asked to provide a blood sample and allow continued access to their medical records. However, as noted, there is some participation bias. As is commonly seen in population-based epidemiologic studies, males were significantly less likely to participate than females, as were residents with fewer medical diagnoses. Since we have

information about who chose not to participate, it will be possible to weight the data statistically when we want to make estimates about population prevalence or incidence of disease. In comparison with the Wood County Census data, it appears that there will be no substantial bias in age or ethnicity in the PMRP cohort. As is commonly seen in epidemiologic studies, current smokers were less likely to participate in the PMRP (18.3% current smokers in PMRP versus 22% current smokers in Wisconsin in 2003 in the Behavioral Risk Factor Surveillance System [26]). Given that the primary ‘exposure’ of interest in the case-control studies to be conducted with the PMRP database is genotype (or haplotype), it is improbable that we will have a systematic bias because adults are unlikely to have chosen to participate or not based on their genetic make-up. Another major advantage of the PMRP is the plan to make the resource available to scientists from other institutions. This should help to foster research collaborations and hopefully support validation of research results in other study populations in a timely manner.

In conclusion, the PMRP will allow researchers to study the genetic basis of disease and drug response in a way that can be generalized to adults of central and northern European descent. We advocate the planning and initiation of similar studies in other ethnic groups and are willing to share our experiences and methodologies so that results are comparable across study populations.

#### Bibliography

1. Watson JD, Crick FHC: Molecular structure of nucleic acids. A structure for deoxyribose nucleic acid. *Nature* 171, 737–738 (1953).
- **The seminal paper by Watson and Crick where they describe the double-helical structure of DNA. Any scientists in the diverse area of genomics research who have not read this short paper should make a point of reading it.**
2. Collins FS, Green ED, Guttmacher AE, Guyer MS, US National Human Genome Research Institute: A vision for the future of genomics research. A blueprint for the genomic era. *Nature* 422, 835–847 (2003).
- **This paper, written by the Director of the NHGRI and colleagues, outlines their vision of the future of human genome research after the completion of the Human Genome Project. It is likely to guide policy and funding decisions for years to come.**
3. Risch NJ: Searching for genetic determinants in the new millennium. *Nature* 405, 847–856 (2000).
4. Lohmueller KE, Pearce CL, Pike M, Lander ES, Hirschhorn JN: Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. *Nat. Rev. Genet.* 3, 177–181 (2003).
- **One of many recent reviews of genetic association studies. Of note is the summary by the authors that the low replication rate for genetic association studies supports the hypothesis that common variants contribute to complex diseases and large study samples are needed to replicate study results.**
5. Long AD, Langley CH: The power of association studies to detect the contribution of candidate genetic loci to variation in complex traits. *Genome Res.* 9, 720–731 (1999).
6. Carson CS, Eberle MA, Rieder MJ, Smith JD, Kruglyak L, Nickerson DA: Additional SNPs and linkage-disequilibrium analyses are necessary for whole-genome association studies in humans. *Nat. Rev. Genet.* 3, 518–521 (2003).
7. Ioannidis JPA, Ntzani EE, Trikalinos TA, Contopoulos-Ioannidis DG: Replication validity of genetic association studies. *Nat. Rev. Genet.* 2, 306–309 (2001).
8. Hirschhorn JN, Lohmueller K, Byrne E, Hirschhorn K: A comprehensive review of genetic association studies. *Genet. Med.* 4, 45–61 (2002).

9. Hirschhorn JN, Altshuler D: Once again – issues surrounding replication in genetic association studies. *J. Clin. Endocrinol. Metab.* 87, 4438–4441 (2002) (Editorial).
10. Altmüller J, Palmer LJ, Fischer G, Scherb H, Wjst M: Genomewide scans of complex human diseases: true linkage is hard to find. *Am. J. Hum. Genet.* 69, 936–950 (2001).
11. Beskow LM, Burke W, Merz JF *et al.*: Informed consent for population-based research involving genetics. *JAMA* 286, 2315–2321 (2001).
  - **Summarizes the recommendations of an expert panel convened by the Centers for Disease Control and Prevention (CDC) to review informed consent for population-based genetic research. Included in this article are templates for a written informed consent document and supplemental brochure for use by researchers.**
12. Deschênes M, Cardinal G, Knoppers BM, Glass KC: Human genetic research, DNA banking and consent: a question of 'form'? *Clin. Genet.* 59, 221–239 (2001).
  - **An opinion piece about the elements that should be included in an informed consent document for human genetic research. The project commenced with a review of existing written informed consent documents. A draft consent form for genetic research and DNA banking is included in the appendix.**
13. Licinio J, Wong M-L: Informed consent in pharmacogenomics. *Pharmacogenomics J.* 2, 343–344 (2002).
14. Clayton EW: Ethical, legal, and social implications of genomic medicine. *N. Engl. J. Med.* 349, 562–569 (2003).
  - **One paper in an excellent series of articles published in the *New England Journal of Medicine* under the banner 'Genomic Medicine'. It summarizes current issues related to genetic discrimination and the appropriate use of genetic information, including case examples.**
15. Anderlik MR: Commercial biobanks and genetic research. *Am. J. Pharmacogenomics* 3, 203–215 (2003).
16. Austin MA, Harding S, McElroy C: Genebanks: a comparison of eight proposed international genetic databases. *Community Genet.* 6, 37–45 (2003).
17. Austin MA, Harding SE, McElroy CE: Monitoring ethical, legal, and social issues in developing population genetic databases. *Genet. Med.* 5, 451–457 (2003).
18. Winickoff DE, Winickoff RN: The charitable trust as a model for genomic biobanks. *N. Engl. J. Med.* 349, 1180–1184 (2003).
19. Commission de l'Éthique de la Science et de la Technologie: *The Ethical Issues of Genetic Databases: Towards Democratic and Responsible Regulation*. Government of Canada, Quebec, Canada (2003).
20. Nuffield Council on Bioethics: *Pharmacogenetics. Ethical Issues*. The Dorset Press, Dorchester (2003).
21. Wang SS, Fridinger F, Sheedy KM, Khoury MJ: Public attitudes regarding the donation and storage of blood specimens for genetic research. *Community Genet.* 4, 18–26 (2001).
  - **Reports the results of a survey of the attitudes of 2621 adults regarding donation and storage of blood specimens for genetic research. More than 20% of the respondents were unwilling to donate blood or have their blood stored for genetic research under any circumstances. These results have implications for the ongoing debate about obtaining informed consent for research using stored tissue samples.**
22. McQuillan GM, Porter KS, Agelli M, Kington R: Consent for genetic research in a general population: the NHANES experience. *Genet. Med.* 5, 35–42 (2003).
23. Knoppers BM: Population genetics and benefit sharing. *Community Genet.* 3, 212–214 (2000).
24. DeStefano F, Eaker ED, Broste SK *et al.*: Epidemiologic research in an integrated regional medical care system: the Marshfield Epidemiologic Study Area. *J. Clin. Epidemiol.* 49, 643–652 (1996).
25. Ciulla Y, Sklar R, Hauser S: A simple method for DNA purification from peripheral blood. *Anal. Biochem* 174, 485–488 (1988).
26. US Census Bureau: *2000 Census of Population and Housing, Summary Population and Housing Characteristics, PHC-1-51, Wisconsin*. US Department of Commerce, Washington DC (2002).

Websites

101. [www.ncbi.nlm.nih.gov/genome/seq/](http://www.ncbi.nlm.nih.gov/genome/seq/)  
The NCBI's Human Reference Sequence site.
102. [www.mfldclin.edu/pmrp/](http://www.mfldclin.edu/pmrp/)  
MCRF – Personalized Medicine Research Center Project website.
103. <http://apps.nccd.cdc.gov/brfss/display.asp?cat=TU&yr=2003&qkey=4394&state=WI>  
The CDC's Behavioral Risk Factor Surveillance System Prevalence Data site (accessed October 25, 2004).

Appendix I – Written informed consent document

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**Research Consent/Authorization Form**  
Marshfield Clinic Research Foundation  
A Division of Marshfield Clinic  
1000 N Oak Avenue, Marshfield, WI 54449  
SP Code: CAL10102+ PI: Michael Caldwell, M.D.

**Title: Personalized Medicine Research Project**

***What is informed consent?***

Informed consent means you understand procedures, risks, possible benefits, and alternatives before you voluntarily agree to participate in a research project. You need to understand if or how the project may affect you and your family. This form and the explanation by project researchers will help you make an informed decision.

You are not giving up any legal rights by signing this consent form to take part in this project. You can withdraw consent at any time.

Please ask research staff about any information you do not understand.

***Why have you been asked to take part in this research project?***

You are invited to participate in this research project because you live in one of 24 zip code areas in northern and central Wisconsin selected for this project. You also receive your healthcare at Marshfield Clinic.

***Why is this research project being done?***

Many, if not most, common diseases have an inherited, or genetic, component. Recent advances have led researchers to believe that even subtle genetic differences between individuals often play an important role in the development of disease and response to treatment. For example, some patients experience severe side effects after taking a particular drug while others do not experience any side effects after taking the same drug.

The ultimate goal of this project is to learn how to apply genetic science to human health. The project will attempt to accomplish this in part by creating a Personalized Medicine Research Database. The database will then be used for multiple studies. Examples of the types of studies, which could use the database, include determining genes responsible for common diseases and determining genes that predict patient's responses to medicines, including adverse reactions. Additional studies could examine how environmental factors and genetic factors interact to cause disease or could determine the distribution and importance of genetic variations.

The project will collect three types of information about each volunteer project participant. These information types are: genetic, which will come from analysis of blood samples; medical, which will come from information contained in medical records; and environment, background, and family information, which will come from a questionnaire. By comparing the genetic information, medical information, and information from the questionnaire, we hope to develop new tests or treatments to improve patient care. All information in the database is guarded by a series of measures described below to assure confidentiality.

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Appendix I – Written informed consent document (continued)

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The consent you are signing will give the researchers permission to collect this information, enter it into the database, perform the genetic analysis on your blood and to analyze information in the database.

***How many subjects will be in this research project, and how long will it last?***

The goal is for over 40,000 people to participate in this project. We anticipate the research project will last for at least 20 years to allow investigators to follow the health of a large population of a defined geographic region over time.

***What are the possible benefits of the research project to you?***

You should not expect to receive any direct benefit from this research project. New knowledge resulting from this project will be made available to the medical community through publications. No information on an individual participant will be released. A possible benefit you could experience would be if tests or therapies are incorporated into medical practice in the future and physicians make use of that new knowledge when caring for patients. And you may experience satisfaction from participating in research that may benefit medical science.

***What will happen if you agree to take part in the Personalized Medicine Research Project?***

You will be asked to donate a blood sample, provide some information through a questionnaire, and agree to the confidential transfer of information from your electronic medical record into a research database.

By agreeing to be in this project, you are agreeing to allow the study investigators and research staff at Marshfield Clinic and Marshfield Clinic Research Foundation to use this information for purposes of this project. Investigators and study staff may also make identifiable data from this project available to the Institutional Review Board or governmental regulatory agencies who may request information for purposes of reviewing the data for accuracy. We intend to use the data collected in this database indefinitely.

Study staff will draw 45 to 50 cc of your blood (approximately four tablespoons). Over the next few years for purposes of this research, researchers will analyze different components of your blood, including your DNA. DNA (deoxyribonucleic acid) is found in blood and is made up of chemicals, arranged in a specific order or sequence, that make up genes.

The questionnaire will ask you for information about yourself and your environment. Since diseases often run in families, it will also ask you to identify members of your immediate family. This family information will be coded in a way that allows researchers to establish family relationships among those people who have volunteered to be in the project.

A research coordinator will also measure your height and weight and enter this information on the questionnaire.

Research project staff will review your medical record. Selected clinical information from your medical record will be transferred into the research database. Research Date approved – May 12, 2003

Appendix I – Written informed consent document (continued)

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project staff may review medical record text notes to confirm the accuracy of the information entered into the database. During the entire study period research staff will continue to gather information from your medical record to enter into the research database. This will allow us to follow your health over time to better define associations among medical conditions, genetic factors, and your environment. Because we are trying to correlate genetic information to medical information, the research database will be updated from your medical record over the life of the study.

***How will privacy and confidentiality of your genetic, medical, and other personal information be protected?***

The results of your DNA analysis will not be entered into your medical record. In accordance with the laws of the State of Wisconsin, these results will not be released to employers or insurance companies. Your DNA sample will not be available for clinical diagnostic purposes. DNA analysis results will not even be shared with you or your family. Any records and research material that would identify you will be held confidential to the full extent allowed by federal and state law.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research.

All information entered into the research database will be coded to protect your privacy. For example, your DNA sample will be identified with a code and not personally identifiable information, such as your name, medical history number, or social security number. And to further enhance confidentiality, the genetic information from your blood sample will be placed in the research database through an encryption (coding) process. Information from your medical record and the questionnaire will not contain personally identifiable information when it is entered into the research database. This medical information will be encrypted using the same coding method as used on the genetic information. Also, project staff having access to identifiable medical record information will not have access to genetic information.

If you join this study, you may stop at any time. Discontinuing your participation involves no penalty or loss of benefits to which you are entitled. Study staff is required by law to obtain a written request from you to document the fact that you chose to withdraw. Research staff will discuss this with you and document your decision on a form, which you will be asked to sign. If you decide to withdraw your permission to continue in this project, the law allows us to continue to use information obtained prior to the time you withdrew your permission if that information is necessary to maintain the integrity of the research project. If you withdraw your permission, we will not collect any additional information about you unless you agree.

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Appendix I – Written informed consent document (continued)

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There is a federal law called the HIPAA Privacy Rule that requires us to keep your medical information private and confidential to the greatest extent possible. In Wisconsin, state law also requires confidentiality of medical information. However, not everyone with whom we share your information may be required to follow this federal law, or they may reside in different states with different laws. Therefore, although the groups we work with are very professional and take confidentiality seriously, we cannot guarantee that the data we share with others will be protected by the same rules.

The Personalized Medicine Research Database will be kept on a separate computer system that will not be connected with other Clinic information systems or to any external network, such as the Internet. The computer will be housed in a highly secure location. Only a limited number of staff will have access to the research database. Only a few individuals will have access to the encryption codes, which will be kept in a separate and secure location. Use of the encryption codes to identify individuals in the database will only be done with approval of the Institutional Review Board, which is responsible for protecting human research subjects. Only with this approval can the researcher determine the identity of a project participant.

***If you take part in the project, who may have access to your study information?***

Marshfield Clinic researchers and research staff authorized to work on this project will have access to your records. They may send portions of your DNA or your genetic information, medical information, or questionnaire information contained in the database to outside researchers or institutions such as, other medical research facilities, or pharmaceutical companies for additional research studies. All such information will have identifying information removed and will be coded.

Federal governmental regulatory or health agencies, and the Marshfield Clinic Institutional Review Board, if required to audit this research project, may be able to see pertinent sections of research records that contain your name or other personally identifiable information. These organizations and people must keep the information private as required by law. Your name will not be given to anyone not associated with this project unless required by law.

The results of this project may be presented at scientific meetings or in scientific publications; however, your identity will not be disclosed.

***What are the possible risks and discomforts of the project?***

The risks of having blood taken from your vein may include bruising, minor pain, infection at the site where the blood was taken or fainting. There will be the usual discomfort of a needle stick.

As noted above, we have designed the project with multiple safeguards to protect your privacy and confidentiality. In addition we will not be releasing information about you to you or your physician, to decrease the risk of accidental release or harmful use of any information coming from this research. There is, nevertheless, a very small chance your personal information could accidentally become known to you, your doctor, or others. In this case information could potentially be used to discriminate against you socially, in insurance, employment or other areas. While Wisconsin laws prohibit

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discrimination based on genetic testing, they do not apply to all types of genetic information and are difficult to enforce.

If you accidentally become aware of information that you have an increased risk of developing a condition, it may have a harmful psychological effect on the way you think about your future. It could also affect your relationship with family members, especially if this changes their risk. If your genetic information reveals certain family circumstances (such as paternity or adoption) and this information becomes known to you or your family, it may also create psychological or social problems for you or your family. However, the risk of any of these events is remote.

It is possible that this project will show that individuals with certain physical characteristics may be at higher risk of developing certain conditions than others. If this happens and that information were released, you may be labeled or treated differently because of these differences including your racial or ethnic characteristics.

This consent form describes the known risks of research in which DNA samples are used. There may also be unknown risks of such research.

***Alternatives to this project.***

You do not have to be in this project to get medical care at any of the participating sites.

***What are the costs for taking part in this project?***

There is no cost to you to take part in this research project. Neither you nor your insurance company will be billed for study related procedures.

***Will you receive any payment for taking part in the project?***

You will receive twenty dollars (\$20) for participating in this study.

***Will any commercial products be developed as a result of this project?***

Research findings from this study may result in knowledge that allows for the development of products that may be of commercial value, on which Marshfield Clinic may for example hold patents. If this happens, there are no plans to provide financial or other types of compensation to you. Like other academic and not for profit institutions, such intellectual property would be owned by Marshfield Clinic and may be licensed for fees. These fees will only be used to pay research expenses, fund additional research and education, provide incentives to the discoverers or inventors at a level consistent with comparable academic and not for profit institutions, donate to healthcare related charities or community healthcare programs, or for other purposes consistent with Marshfield Clinic's not for profit mission. If any products are developed from this project that are of commercial value, a portion of the financial proceeds from such products will be donated to charities and Wisconsin communities to help pay for healthcare for the poor, public health programs, or other healthcare related programs.

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Appendix I – Written informed consent document (continued)

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***Emergency care and compensation for injury.***

If you become ill or injured from this study, medical care is available at Marshfield Clinic, St. Joseph's Hospital or other medical facilities. You or your health insurer would be responsible for this cost. This facility has no plans to compensate you for such illness or injury, financially or otherwise.

***Do you have to take part in this project?***

You do not have to take part in this research project. If you choose not to participate, your relationship with your doctors or this facility will not change. You will not lose benefits to which you would otherwise be entitled to. The decision will not affect your future medical care.

***Will your relatives be contacted?***

Your relatives may be contacted independently to participate in this project if they are in the population already defined for the study. They will not be contacted because of information you have provided.

***Will the results of this project be shared with you?***

No information resulting from the analysis of your DNA or about your genetic status, such as the probability of developing a specific disease, will be provided to you. Research results are often preliminary, inconclusive, and not necessarily valid for decisions concerning patient care and treatment. Preliminary information, if given to you, could create false conclusions and significant risks.

Researchers will periodically send a newsletter to all project subjects. The newsletter will not contain any individual results, but will contain general information about studies. We will ask you to inform the project staff of any changes to your mailing address so that you continue to receive the newsletter.

\_\_\_\_\_ Initial here if you do NOT want to receive copies of the newsletter.

***Will you ever be re-contacted for additional information?***

This project will last many years. Since we will be comparing genetic information to medical and questionnaire information, you should expect to be re-contacted occasionally to update the questionnaire information. This will occur at different times for different people and would not imply that anything has been learned about you specifically.

Researchers may want to re-contact you for an additional blood sample. Your DNA will be saved for as long as possible, hopefully for many years. Over time, the DNA may be entirely used or deteriorate through storage. Also, new and more accurate methods of genetic analysis may become available, requiring different processing of blood samples or other genetic material in the future. You may be asked to sign a new consent at that time.

This database will be used for many studies. New information or knowledge will cause new research questions to be asked, and new and different studies designed to answer  
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Appendix I – Written informed consent document (continued)

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them. If any such study has a different design than this project, and would create risks not considered in this consent, the Institutional Review Board would require the researchers to inform you of these risks and ask you to sign a separate consent for this separate study. You would be under no obligation to participate.

\_\_\_\_\_ Initial here if you do NOT want researchers to re-contact you regarding future research studies.

***Can you withdraw from this project and what will happen to your DNA sample and medical information if you withdraw?***

By federal law you have the right to withdraw at any time and leave this project. There are two ways to withdraw from this project. One is to ask researchers to destroy any of your remaining DNA. The other is to ask that your DNA be destroyed and that all of your information already entered in the research database be removed.

You may withdraw your consent for research staff to re-contact you in the future at any time.

If you decide to withdraw from the project entirely, or withdraw your consent to be re-contacted, you will need to provide researchers a written statement that you no longer wish to participate and which method of withdrawal, you wish to use.

***Who can you call if you want more information about this project?***

For more information about this research project or to report injuries or side effects, you may contact the research coordinators or investigators of the Personalized Medicine Research Project, Marshfield Clinic Research Foundation, at 715-387-9433.

If you have any questions about your rights as a research subject, you may contact Marshfield Clinic Research Foundation's Institutional Review Board (IRB) at 1-800-782-8581 ext. 9-3022.

***What does signing this consent form mean?***

A signature indicates that:

- You have read the above.
- You have freely decided to take part in the research study described above.
- The study's general purposes, details of involvement and possible risks and discomforts have been explained to you.

You will receive a signed copy of this consent form.

\_\_\_\_\_  
Signature of Participant  
(If able to give informed consent.)

\_\_\_\_\_  
Date

\_\_\_\_\_  
Printed Name of Participant

.....OR.....

Date approved – May 12, 2003

Appendix I – Written informed consent document (continued)

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\_\_\_\_\_  
Signature of Health Care Agent as Designated by \_\_\_\_\_ Date \_\_\_\_\_  
Power of Attorney for Health Care.....**OR**....  
Court-Appointed Guardian **(Circle appropriate title.)**

Reason participant was unable to give informed consent: \_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_  
Printed Name of the Above Signature .....**AND**.....

\_\_\_\_\_  
Signature of Presenter (Investigator or Designee) \_\_\_\_\_ Date \_\_\_\_\_

\_\_\_\_\_  
Printed Name of Presenter

06/04/2002; 06/28/2002; 07/19/2002; 07/24/2002; 01/22/2003; 02/07/2003; 04/23/2003;  
05/12/2003  
H:\RADMIN\CONSENT FORMS\A-H\CAL10102.DOC  
See also: H:\RADMIN\CONSENT FORMS\A-H\CAL10102 Watermarked.doc  
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Date approved – May 12, 2003

Appendix II – Flyer developed in consultation with the Community Advisory Group to promote the Personalized Medicine Research Project



**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 **1-888-334-2232** 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.”*

**Fire Chief Jerry Minor**

*(back row) Jim Churchill, Bob Wolff  
(front row) Larry Wolf, Jerry Minor, Paula Hensel*

  
**MARSHFIELD CLINIC®**  
*Where the future of medicine lives*

99.0729

Copyright of the PMRP flyer in Appendix II is retained by the Marshfield Clinic Research Foundation.

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## Marshfield Clinic Personalized Medicine Research Project Information Sheet

Please fill in this form as completely as possible. We understand you may not know all of the information requested. Leave blank any items about which you are not certain. Using a black pen or pencil, please completely darken circles and print clearly.

Many diseases are thought to result from a combination of both environmental and genetic factors. We are asking you to provide information about your environment, race and ancestry, and major diseases and adverse reaction to medications that may be common in your family. The environmental information will help researchers better understand health risks and may assist in developing preventive programs. Race and ancestry information will help researchers identify genetic risk factors that are specific to individual populations. Family information is crucial because close biological relatives share similar genetic information, which explains why some diseases and serious reactions to medications may run in the same family. Researchers study health and disease in families to understand these genetic influences better.

This questionnaire will be treated as a confidential medical record and stored securely. The information concerning you and your family will be stripped of your name and other identifiers and will be entered into a secure, coded research database at Marshfield Medical Research Foundation. Access to this database will be limited to qualified Marshfield Clinic researchers approved by the Marshfield Clinic Institutional Review Board. Your responses are voluntary. You are not required to answer questions that make you feel uncomfortable, but all answered questions will help out in our research.

© 2002 Marshfield Medical Research Foundation  
1000 North Oak Avenue, Marshfield, WI 54449  
Attention: Personalized Medicine Research Project  
715-389-7733 or 888-334-2322  
[www.mfclin.edu/pmrp](http://www.mfclin.edu/pmrp)

Appendix III – Personalized Medicine Research Project  
baseline questionnaire (continued)

Name: \_\_\_\_\_

Using a black pen or pencil, please completely darken circles and print clearly.

1. What is your race?  
(Mark one or more to indicate what you consider yourself to be.)
- White Caucasian
  - Black, African American, or Negro
  - American Indian
  - Asian/Hmong
  - Hispanic/Latino/Spanish
  - Other \_\_\_\_\_ Please Print
2. How would you describe your ancestry or ethnic origin?  
(You may list more than one, if applicable).
- Czech
  - Irish
  - Dutch
  - Norwegian
  - English
  - Polish
  - French/French Canadian
  - Swedish
  - German
  - Other \_\_\_\_\_ Please Print

3. Where do you currently live most of the year?
- On a working farm or ranch
  - In a rural home or hobby farm, not a working farm or ranch
  - In a suburb, city, or village
  - Other \_\_\_\_\_ Please Print

4. Have you ever lived on a working farm?

- Yes
- No

Research Coordinator Use

\_\_\_\_\_

Ethnicity Code

\_\_\_\_\_

Survey Code Office Use Only

Appendix III – Personalized Medicine Research Project  
baseline questionnaire (continued)

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5. The following three questions concern smoking of cigarettes:
- a. Have you smoked at least 100 cigarettes in your entire life?  
 Yes  
 No (Go to Question 6)
- b. Do you now smoke cigarettes every day, some days or not at all?  
 Every day  
 Some days  
 Not at all (Go to Question 6)
- c. On days that you smoke, about how many cigarettes a day do you smoke, on the average?  
 For example, if you smoke 10 cigarettes per day fill in the following circles: 0 1 0
- |         |   |   |   |   |   |   |   |   |   |   |
|---------|---|---|---|---|---|---|---|---|---|---|
|         | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|         | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Example | ● | ● | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
6. The following three questions concern alcohol use:
- a. During the past month, have you had at least one drink of any alcoholic beverage, such as beer, wine, wine coolers, or liquor?  
 Yes  
 No (Go to next section and Question 7)
- b. During the past month, on how many days per week did you drink any alcoholic beverages, on the average?  
 < 1  
 1-2  
 3-4  
 5-7
- c. On the days during the past month when you drank alcoholic beverages, about how many drinks per day did you drink, on the average?  
 0  
 1  
 2  
 3-4  
 5 or more

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Appendix III – Personalized Medicine Research Project  
baseline questionnaire (continued)

We would like to find out if certain diseases are common in your family. Please tell us if you know that at least 2 or more blood relatives in your immediate family (including yourself) have been diagnosed with any of the following conditions. Your immediate blood relatives include yourself, your mother and father, your brothers and sisters, and your biological children. They do NOT include relatives by marriage, stepbrothers and sisters, parents by adoption, stepchildren, adopted children, grandparents, aunts, uncles, or cousins.

We do NOT want you to identify the individuals who have these conditions—we just want to find out if any of the diseases run in your family. If you do not want to provide this information, you can leave this section blank.

7. Condition Diagnosed in 2 or more immediate blood relatives (including yourself)?

- |                        |                           |                          |                                  |                             |                           |                          |                                  |
|------------------------|---------------------------|--------------------------|----------------------------------|-----------------------------|---------------------------|--------------------------|----------------------------------|
| a. Alzheimer's disease | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know | p. Emphysema                | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know |
| b. Arthritis           | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know | q. Epilepsy                 | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know |
| c. Asthma              | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know | r. Glaucoma                 | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know |
| d. Blindness           | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know | s. Heart attack or angina   | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know |
| e. Breast cancer       | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know | t. Congestive heart failure | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know |
| f. Cervical cancer     | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know | u. High blood pressure      | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know |
| g. Colon cancer        | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know | v. Kidney disease           | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know |
| h. Lung cancer         | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know | w. Liver disease            | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know |
| Melanoma of the skin   | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know | x. Lupus                    | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know |
| j. Oral cancer         | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know | y. Mental disorders         | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know |
| k. Prostate cancer     | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know | z. Multiple sclerosis       | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know |
| Other type of cancer   | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know | aa. Stroke                  | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know |
| m. Chronic bronchitis  | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know | bb. Thyroid disorders       | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know |
| n. Crohn's disease     | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know |                             |                           |                          |                                  |
| o. Diabetes            | <input type="radio"/> Yes | <input type="radio"/> No | <input type="radio"/> Don't Know |                             |                           |                          |                                  |

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Appendix III – Personalized Medicine Research Project  
baseline questionnaire (continued)

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*Sometimes a person's genetic make-up can affect the response to medications.*

8. In the past 10 years, have you ever had a serious reaction to a doctor-prescribed medicine or over-the-counter medication that was received either by mouth or by injection?

- Yes
- No

This includes problems that required a doctor visit or admission to a hospital. It does NOT include problems that were managed at home.

- Yes
- No (Go to Question 14)
- Don't Know (Go to Question 14)

11. Did a Marshfield Clinic doctor provide medical care for this reaction?

- Yes (Go to Question 13)
- No (Go to Question 12)

9. If yes, what type of reaction?

- Rash
- Swelling
- Breathing problems
- Other

Please Print

12. What was the name of the medication that caused the reaction?

\_\_\_\_\_

or

- Don't Remember

13. Have any of your immediate blood relatives (parents, brothers, sisters, and children) ever had a serious reaction to the SAME medicine that caused your reaction?

- Yes
- No
- Don't Know

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Appendix III – Personalized Medicine Research Project  
baseline questionnaire (continued)

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14. Were you employed in the past 5 years?

- Yes
- No (If no, skip Questions 15 and 16.)

15. What is the nature of the businesses or industries where you have worked during the past 5 years? Please select the one category that fits best for each business or industry.

- Agriculture, Forestry, Fishing, and Hunting
- Mining
- Utilities
- Construction
- Manufacturing
- Wholesale Trade
- Retail Trade
- Transportation and Warehousing
- Information and Communications
- Finance, Insurance, Real Estate, and Rental and Leasing
- Services: Professional, Scientific, Management, and Administrative
- Services: Waste Management
- Services: Educational, Health, and Social
- Services: Arts, Entertainment, Recreation, Accommodations, and Food
- Services: Other (except Public Administration)
- Public Administration
- Active Duty Military

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Appendix III – Personalized Medicine Research Project  
baseline questionnaire (continued)

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16. What has your occupation been during the past 5 years? (What kind of work have you done for your employer(s)?) Please select the one category that fits best for each job.

- Management (e.g., Executive, Sales Manager, Educational Administrator)
- Business Operations Specialists (e.g., Buyer, Claims Adjuster, Human Resource Specialist)
- Financial Specialists (e.g., Accountant, Insurance Underwriter, Real Estate Appraiser)
- Computer and Mathematical Occupations (e.g., Computer Support, Systems Analyst, Actuary)
- Architecture and Engineering (e.g., Architect, Drafter, Chemical Engineer, Surveyor)
- Life, Physical, and Social Science Occupations (e.g., Medical Scientist, Chemical Technician, Urban Planner, Psychologist)
- Community and Social Service (e.g., Counselor, Religious Worker, Social Worker)
- Legal Occupations (e.g., Lawyer, Magistrate, Legal Assistant or Support)
- Education, Training, and Library Occupations (e.g., Teacher, Teacher Assistant, Archivist, Librarian)
- Arts, Design, Entertainment, Sports, and Media Occupations (e.g., Choreographer, Umpire, Editor, Camera Operator)
- Healthcare Practitioners and Technical Occupations (e.g., Physician Assistant, Clinical Laboratory Technologist, Paramedic)
- Healthcare Support (e.g., Medical Assistant, Home Health Aide, Massage Therapist)
- Protective Services (e.g., Police Officer, Crossing Guard, Fire Inspector)
- Food Preparation and Serving (e.g., Cook, Waiter, Dishwasher, Restaurant Hostess)
- Building and Grounds Clearing and Maintenance (e.g., Janitor, Landscape Worker, Pest Control)
- Personal Care and Service (e.g., Fitness Worker, Child Care Worker, Tour Guide, Funeral Service Worker)
- Sales (e.g., Cashier, Travel Agent, Model, Real Estate Broker, News Vendor)
- Office and Administrative Support (e.g., Receptionist, Billing Clerk, Bank Teller, Customer Service Representative)
- Farming, Fishing, and Forestry (e.g., Agricultural Inspector, Logging Worker, Fisher, Farmer/Farm Worker)
- Construction Trades (e.g., Carpenter, Painter, Pipefitter, Roofer, Highway Maintenance)
- Extraction Workers (e.g., Earth Driller, Explosives Worker, Miner)
- Installation, Maintenance, and Repair (e.g., PC Repair, Mechanic, Heating/Air Cond. Repair, Telecomm Line Installer)
- Production Occupations (e.g., Assembler, Baker, Machine Operator, Cabinet Maker)
- Transportation and Material Moving (e.g., Taxi Driver, Service Station Attendant, Industrial Truck/Tractor Operator)
- Military Specific Occupations

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Appendix III – Personalized Medicine Research Project  
baseline questionnaire (continued)

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**To be completed by Research Coordinator at time of appointment:**

Height Inches	Weight lbs	How long since you've last eaten: Hours
<input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> 8 <input type="radio"/> 9	<input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> 8 <input type="radio"/> 9	<input type="radio"/> 0 <input type="radio"/> 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> 8 <input type="radio"/> 9 <input type="radio"/> Patient doesn't remember

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