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Informed Consent and Subject Motivation to Participate in a Large, Population-Based Genomics Study: The Marshfield Clinic Personalized Medicine Research Project

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Ethics · Genomics · Informed consent

Abstract
Background: The objective of this study was to measure subject perspective and reaction to participation in the Personalized Medicine Research Project (PMRP) and to identify factors predicting understanding of the study elements. ***Method:*** Self-administered questionnaires were mailed to 1,593 subjects (10% sample). The questionnaire had three sections: section A consisted of 21 factual questions; section B consisted of 14 questions to assess the level of understanding about the PMRP concepts, and section C asked about the purpose of the PMRP. ***Results:*** The mean age of the 924 survey respondents was 52 years (SD = 16.9), with a range of 18–95 years. The majority of participants were female (n = 561, 61%). The percent of total correct responses for section A was significantly higher for females compared with males (males: 58.4% and females: 60.4%, t test = –2.18, p = 0.03) and age was significantly inversely related to percent of correct responses (β coefficient = –0.122, $p < 0.001$). More than one third of the participants indicated that the USD 20 greatly influenced their decision to participate in the project. In a multiple logistic regression model, people living outside of Marshfield were significantly more likely to indicate that the USD 20 greatly influenced their decision to participate (odds ratio = 1.40, 95% confidence limit = 1.06, 1.86) and age was inversely related to the monetary influence on decision to participate (odds ratio = 0.98, 95% confidence limit = 0.97, 0.98). ***Conclusion:*** Future community consultation efforts should highlight areas of lower understanding. In addition, research coordinators may need to take more time informing males and older individuals about project details so that they are making truly informed decisions about study participation.

The year 2004 represents the 25th anniversary of the release of the Belmont Report from the National Commission for the Protection of Human Subjects of Biomedical Research [1]. This report outlined the three basic ethical principles underlying the acceptable conduct of research involving human subjects: (1) respect for persons, (2) beneficence, and (3) justice. In response to the Belmont Report, the US Department of Health and Human Services and the Food and Drug Administration issued significant revisions to their human subjects regulations. The US Department of Health and Human Services regulations are contained in Title 45, Part 46 of the Code of Federal Regulations. Institutional Review

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Boards (IRBs) at institutions that accept federal funding for research involving human subjects have responsibility for ensuring compliance with these federal regulations. In addition to assessing risk/benefit ratios, IRBs review and approve informed consent documents and the process for achieving informed consent prior to the initiation of research with human subjects. There is a vast body of literature on the quality of informed consent procedures, especially in relation to clinical trials of therapeutic agents. Patient recall and comprehension of informed consent has been shown to be relatively low for both therapeutic and non-therapeutic studies [2, 3] and a number of methods have been proposed, but not uniformly adopted, to improve patient comprehension and recall.

While there are no federal regulations that require IRBs to review and approve compensation for research subjects, IRBs are responsible for ensuring that research participation is voluntary and not coercive. The topic of payment of research subjects has been the subject of much debate in the medical literature, with support often varying by whether there was any possible benefit to the subject [4–8]. Dickert and Grady [4] proposed the adoption of the 'wage payment' model for payment of research subjects, arguing that this model would not involve undue influence, would provide for standardization among studies, and would be equitable to subjects in terms of treating similar people similarly. Forty-three percent of participants surveyed about their attitudes toward payment for research participation agreed with paying either patient or healthy volunteer study participants [5]. The following acceptable conditions for payment were identified by survey respondents: (1) to improve problematic recruitment, (2) to reimburse costs, and (3) to recognize the time investment of participants. A study published in 2004 found no evidence that commonly used payment levels to research subjects served as an undue inducement to study participation [8].

With the completion of the Human Genome Project and the call for large-scale production of genomic data to identify genetic contributions to disease and drug response [9], an emerging issue for investigators and IRBs is the informed consent process for research involving stored tissue samples. The Office for Human Research Protections in the US Department of Health and Human Services released guidance for research involving coded private information and biological specimens [10]. High variability between IRBs in regard to review of genetic studies has been demonstrated [11, 12] and draft templates have been proposed to facilitate standardization of written informed consent documents for genetic research and DNA banking [13, 14].

The purpose of this study was to investigate comprehension of the elements of the informed consent process and to identify the extent to which money was an inducement to participate in a population-based DNA and biorepository.

Methods

Personalized Medicine Research Project (PMRP)

Marshfield Clinic's PMRP, which commenced recruitment in September 2002, aims to establish a database to support research in the areas of genetic epidemiology, pharmacogenetics and population genetics. In phase I, subjects 18 years of age and older, residing in one of 19 zip codes in the Marshfield Epidemiological Study Area [15], and receiving healthcare in any of the Marshfield Centers, were enrolled in PMRP after giving written informed consent. Blood was drawn from each consenting participant and then DNA was extracted and DNA, plasma and serum samples were stored for each participant. Patients and community members gave their consent to participate with the understanding of non-disclosure of personal genetic results. Subjects were informed that a de-identified dataset would be created for analyses. They were given the option of not being recontacted for future studies. A copy of the written informed consent document is available on the Marshfield Clinic public website (http://www.mfldclin.edu/research/pmtext/informedconsent.pdf). Consultation for the PMRP occurred at three levels: (1) an ethics and security advisory group, (2) a scientific advisory board, and (3) a community advisory group. Phase II involves the development of the policies and procedures to allow the PMRP database to be a national resource and phase III will comprise the genetic discovery projects and ongoing provider and community education.

The research study protocol for the PMRP and for the current sub-study were reviewed and approved by the Marshfield Clinic's IRB. For this sub-study of the quality of the informed consent and motivations for study participation, a 10% random sample of the PMRP study participants who had participated from the first day of study recruitment (September 18, 2002) through May 26, 2004, and gave written informed consent to be recontacted for future studies (n = 1,593) was selected to receive a self-administered questionnaire.

Questionnaire

The questionnaire consisted of three sections and was modified from questionnaires used in the areas of cancer clinical trials [16, 17] and genetics [18, 19]. Section A contained 21 questions based on the facts of the study and the content of the informed consent document and process including whether the subject knew that he/she was participating in a research project before signing the consent form, the goals of the study, the fact that individual results would not be released, and the duration of participation. Three additional questions in section A were opinion-based questions on pressures to participate from other individuals and the influence of payment on participation. There were three responses to the questions in section A: (1) disagree, (2) unsure, and (3) agree. Section B

contained 14 questions and used a 5-point scale to assess subject perspective and level of understanding of various aspects of the PMRP including whether the participant understood the information provided, the time commitment, possible risks and benefits, the fact that participation was voluntary, whether the subject felt that participation would benefit future patients and overall understanding of the project. Section C consisted of a single open-ended question ('Please describe in your own words the purpose of the PMRP').

The questionnaire was mailed in a postage-paid envelope to the 10% random sample of PMRP participants. If the completed survey was not returned within 2 weeks, questionnaires were mailed out a second time. Only two mailings were attempted and no incentives were offered for completion of the questionnaire.

After coding of the open-ended question, the data were entered into a Microsoft Excel® spreadsheet. SPSS® was used for the statistical analyses. χ^2 analyses and Fisher's exact tests were used for categorical variables (gender and zip code) and t tests and linear regression models were used for continuous variables (age and days since initial study participation). Binary logistic regression analysis was used to quantify independent predictors of correct and incorrect responses and positive and negative attitudes. Ninety-five percent confidence limits were calculated assuming a binomial distribution.

Results

Questionnaires were returned by 924 PMRP participants (58% response rate). The mean age of survey respondents was 52 years (SD = 16.9), with a range of 18–95 years. The majority of participants were female (n = 561, 61%). Less than half the participants were residing within the Marshfield zip code (n = 376, 41%). The time since participation in the PMRP ranged from 39 days to 636 days, median = 362 days (approximately 1 year).

χ^2 analysis revealed significant differences between participants and non-participants of this sub-study in terms of gender; 54% of males responded, compared to 61% of females ($\chi^2 = 6.494$, $p = 0.012$). Participation also differed significantly by age. The mean age of participants and non-participants was 52 years and 41 years, respectively ($t = 12.819$, $p < 0.001$). There was no significant association between zip code of residence or time since participation in the PMRP and participation in the current sub-study (both $p > 0.10$, data not presented).

The distribution of responses to the statements describing details of the PMRP that were contained in the written informed consent document are summarized in table 1. The statement that almost the entire cohort (99.3%) answered incorrectly was: 'All the procedures in this research project are standard for any routine genetic testing' (correct answer is 'disagree'). The majority of participants (86.4%) also incorrectly indicated that they were unsure or agreed with the statement that 'this research project does not carry any risks or discomforts'. More than half the study cohort also responded incorrectly to the following two statements: 'My DNA will be stored as part of this research study' (82.1% not correct) and 'Because I am participating in a genetics research study, it is possible that the study sponsor, various government agencies, or others who are not directly involved in my care could view my medical records' (76.0% not correct).

Univariate analyses (χ^2 and t tests) were conducted to assess the relationship between gender, age, zip code of residence and time since participation and correct response to the factual statements in section A. Time since participation was significantly related to only one of the 21 statements (question 3), with a mean of 335.3 days since main study participation for those who did agree that they had been informed how long their participation in the project would last, compared with 363.1 days for those who said that they were not informed (t test = 2.82, $p = 0.005$). Age and gender were significantly associated with correct responses for 13 and 11 of the statements in section A, respectively (data not presented). Zip code of residence was a significant factor for correct response to five statements in section A (data not presented). For those questions where at least 10% of the cohort responded incorrectly, logistic regression models that included age, gender and residence (Marshfield resident or not, only included if significant in univariate analyses) were run to assess the independent association between these factors and responding correctly to the statements in section A (table 2). In these multivariate models, age continued to be significantly inversely related with probability of correct responses to eight of the statements in section A, and females were significantly more likely then males to respond correctly to three of the statements.

A total score for correct responses to section A was calculated and then the percent of correct responses was calculated to account for missing responses. Overall, the percent of total correct responses to the factual statements in section A ranged from 0 to 95.2 (mean = 59.6, median = 61.9). The percent of total correct responses for section A was significantly higher for females compared with males (males: 58.4% and females: 60.4%, t test = –2.18, $p = 0.03$), and age was significantly inversely related to percent of correct responses (β coefficient = –0.122, $p < 0.001$), but the r^2 value was relatively low (0.024). Time since participation was not related to percent of correct responses for section A ($r = 0.012$, $p = 0.724$).

Ninety-six percent of the respondents indicated that they did not feel pressured by study personnel or others

Table 1. Distribution of responses to section A

Statement		n	Responses, %		
			disagree	unsure	agree
1	When I signed the consent form to have my blood drawn, I knew that I was agreeing to participate in a research project.	923	0	0.9	**99.1**
2	The main goal of genetic research studies, such as the PMRP, is to improve scientific knowledge for future patients.	922	0.2	1.7	**98.0**
3	I have been informed how long my participation in the PMRP is likely to last.	920	2.3	39.9	**57.8**
4	All the procedures in the research project are standard for any routine genetic testing.	917	**0.8**	33.4	65.9
5	In this research project, one of the major goals is to understand how genes contribute to the development of disease.	918	0.2	7.2	**92.6**
6	In this research project, one of the major goals is to explore the genetic basis for reactions to prescription drugs.	919	6.6	40.4	**53.0**
7	In this research project, one of the major goals is to establish a DNA database for researchers to use.	914	2.3	23.4	**74.3**
8	In this research project, one of the researchers' major purposes is look for genes associated with higher and lower rates of disease.	915	0.7	14.6	**84.7**
9	The genetic testing in this study will result in my learning which conditions/diseases I will develop.	918	**39.0**	33.3	27.7
10	My DNA will not be stored as part of this research study.	918	**18.0**	51.9	30.2
11	As part of this study, researchers will have access to my medical records.	913	20.5	25.8	**53.7**
12	After I choose to participate in this research study, my sample will be labeled with my name in order to identify it.	916	**55.1**	21.0	23.9
13	This research project does not carry any risks or discomforts.	918	**13.6**	12.9	73.5
14	There may not be direct medical benefit to me from my participation in this research study.	913	4.1	12.5	**83.5**
15	By participating in this research study, I am helping the researchers learn information that may benefit future patients.	917	0.1	1.5	**98.4**
16	Because I am participating in a genetics research study, it is possible that the study sponsor, various government agencies, or others who are not directly involved in my care could view my medical records.	920	45.8	30.2	**24.0**
17	The researchers did not offer me any alternative besides involvement in this research study.	914	**49.7**	20.7	29.6
18	The consent form that I signed describes who will pay for my treatment if I am injured or become ill as a result of participation in this research study.	911	16.5	50.9	**32.6**
19	The consent form I signed lists the name of a person (or persons) whom I should contact if I have any questions or concerns about this research study.	917	3.2	30.9	**66.0**
20	If I had not wanted to participate in this study, I could have declined to sign the consent form.	920	0.4	2.5	**97.1**
21	I will have to remain in this research study even if I decide someday that I want to withdraw.	920	**62.3**	26.0	11.7
22	I felt pressured by the study personnel to participate in the PMRP.	912	95.9	2.1	2.0
23	I felt pressured by someone other that the study personnel to participate in the PMRP.	911	95.8	2.1	2.1
24	The USD 20 greatly influenced my decision to participate in the PMRP.	908	60.0	5.7	34.3

Correct responses are in bold. Percentages may not add to exactly 100.0% due to rounding.

Table 2. Predictors of correct responses to factual statements in section A (significant predictors are in bold)

Statement		Predictor, odds ratio (95% confidence limit)			
		age, years	female gender	live outside Marshfield	
3	I have been informed how long participation in the PMRP is likely to last.	**0.98 (0.97, 0.99)**	1.08 (0.82, 1.41)	N/A	N.S.
6	In this research project, one of the major goals is to explore the genetic basis for reactions to prescription drugs.	**1.01 (1.006, 1.02)**	0.93 (0.71, 1.21)	**1.32 (1.01, 1.72)**	
7	In this research project, one of the major goals is to establish a DNA database for researchers to use.	0.99 (0.99, 1.01)	0.96 (0.71, 1.29)	**0.65 (0.48, 0.89)**	
8	In this research project, one of the researchers' major purposes is to look for genes associated with higher and lower rates of disease.	0.99 (0.98, 1.00)	1.41 (0.99, 2.00)	N/A	N.S.
9	The genetic testing in this study will result in my learning which conditions/diseases I will develop.	**0.98 (0.97, 0.98)**	**1.38 (1.04, 1.83)**	N/A	N.S.
10	My DNA will not be stored as part of this research study.	**0.98 (0.97, 0.99)**	0.93 (0.66, 1.32)	N/A	N.S.
12	After I choose to participate in this study, my sample will be labeled with my name in order to identify it.	**0.98 (0.97, 0.983)**	**1.34 (1.02, 1.76)**	N/A	N.S.
13	This research project does not carry any risks or discomforts.	**0.97 (0.96, 0.99)**	0.78 (0.53, 1.15)	N/A	N.S.
16	Because I am participating in a genetics research study, it is possible that the study sponsor, various government agencies, or others who are not directly involved in my care could view my medical records.	**1.009 (1.00, 1.02)**	0.90 (0.66, 1.22)	N/A	N.S.
17	The researchers did not offer me any alternatives besides involvement in this research study.	**0.97 (0.96, 0.98)**	1.09 (0.83, 1.44)	0.77 (0.58, 1.01)	
19	The consent form I signed lists the name of a person (or persons) whom I should contact if I have any questions or concerns about this research study.	**0.99 (0.98, 0.999)**	**1.48 (1.13, 1.96)**	N/A	N.S.
21	I will have to remain in this research study even if I decide someday that I want to withdraw.	**0.99 (0.98, 0.997)**	1.04 (0.79, 1.37)	N/A	N.S.

N.S. = Not significant in univariate analyses.

to participate in the study (table 1). More than one third of the participants indicated that the USD 20 greatly influenced their decision to participate in the project. In a multiple logistic regression model, people living outside of Marshfield were significantly more likely to indicate that the USD 20 greatly influenced their decision to participate (odds ratio = 1.40, 95% confidence limit = 1.06, 1.86) and age was inversely related to monetary influence on decision to participate (odds ratio = 0.98, 95% confidence limit = 0.97, 0.98). The participants who indicated that they felt pressured by someone other than study personnel to participate in PMRP were significantly more likely to indicate that the USD 20 greatly influenced their decision to participate (60.5 vs. 38.8%, $\chi^2 = 7.21$, $p = 0.007$).

In section 2, participants were asked to indicate the level of understanding they felt about various components of the PMRP (table 3). For two of the 14 concepts, less than half of the study population circled numbers 4 or 5, the highest levels of understanding. These two least-well-understood concepts were: (1) which of the procedures are experimental (43.3% level 4 or 5), and (2) who will pay for the treatment if you are injured or become ill as part of this research study (48.4% level 4 or 5). A total score for level of understanding was calculated by summing the responses to all 14 statements. The percent of total possible was calculated to account for missing responses. Overall, the percent of understanding of statements in section B ranged from 28.6 to 100%, with a mean of 81.4% (SD = 13.6). As with section A, the level of understanding varied by age and gender. The mean level of

Table 3. Distribution of responses to level of understanding of concepts in section B

	Concept	n	Level of understanding, %				
			1	2	3	4	5
1	The fact that the PMRP involves genetic research.	913	0.7	1.3	7.9	20.2	69.8
2	What the researchers are trying to find out in the PMRP.	913	1.1	3.5	21.1	36.9	37.1
3	How long you will be in the research study.	909	4.2	9.5	32.9	24.3	29.2
4	The procedures you will undergo as part of the study.	909	3.3	5.1	22.2	26.6	42.7
5	Which of the procedures are experimental.	897	9.6	11.5	35.6	22.5	20.8
6	The possible risks and discomforts of participating in the PMRP.	909	3.9	4.0	17.9	26.3	48.0
7	The possible benefits to you of participating in the PMRP.	909	2.8	3.2	16.1	31.2	46.8
8	How your participation in the PMRP may benefit future patients.	913	0.7	1.1	5.9	26.2	66.2
9	The alternatives to participation in the PMRP.	902	7.4	7.4	25.6	20.3	39.2
10	How the confidentiality of my records will be protected under the PMRP.	909	2.4	2.2	12.5	28.2	54.7
11	Who will pay for treatment if you are injured or become ill as part of this research study.	902	8.3	11.6	31.5	18.4	30.0
12	Whom should you contact if you have questions or concerns about the PMRP.	910	4.3	6.6	21.0	23.5	44.6
13	The fact that participation in the PMRP is voluntary.	914	0.8	0.3	2.6	10.3	86.0
14	Overall, how well did you understand the PMRP when you signed the consent form.	907	0.8	2.0	16.3	42.7	38.1

Level of understanding: from 1 (not at all) to 5 (very well). Percentages may not add to exactly 100.0% due to rounding.

understanding was 79.6% for males, compared with 82.6% for females (t test = –3.28, p = 0.001). Total level of understanding was inversely associated with age (β coefficient = –0.0623, p = 0.02), however the percent of variance in total understanding explained by age was very small ($r^2 = 0.006$). Self-perceived level of understanding of the concepts in section B was significantly related to the percent of correct responses to section A (β coefficient = 0.538, $p < 0.001$), and this correlation changed only slightly by including age and gender in the regression model (data not presented).

Discussion

This study provides the first detailed information about issues of informed consent and subject motivation to participate in a large, population-based DNA research bank. In general, we found that almost all study participants understood the overall goals of the project, but many were unsure or incorrect about such key issues as the duration of their participation in the study, the fact that their DNA would be stored, and the non-disclosure of personal study results. This has implications for the current study, as well as research in general. We support ongoing research to determine the best way to undertake the consent process and to evaluate that people are making truly informed decisions to participate in research.

The inverse association between the percent of correct responses and age that was observed in the current study is consistent with prior research that has shown that the elderly are less likely to comprehend details of consent information [21], in large part due to readability [22]. Although we did not test comprehension immediately following the informed consent process, our data suggest that the incorrect responses were due to a lack of comprehension rather than a loss of memory of specific details because the percentage of correct responses was not related to the time since participation in the primary study. Several models to improve the informed consent process for elderly subjects have been proposed, including testing and correction of comprehension [23], and matching information to learning style and ability [24]. Our data suggest that additional efforts to ensure truly informed consent may be necessary for older subjects in our population.

The self-perceived level of understanding (81.4%) was greater than the actual correct knowledge in this cohort (59.6%). These percentages are slightly lower than were observed in the NUgene study in Chicago (89.4 and 68.6%, respectively), upon which the current survey was modeled [18]. Although the percentages were somewhat lower for the PMRP than NUgene participants for spe-

cific items, our study results concurred with NUgene that participants had lower understanding of the potential risks and discomforts of the study, the experimental nature of the genetic testing, the procedures involved in the event of an injury and the confidentiality issues. Perhaps because both PMRP and NUgene are observational non-interventional studies, subjects think less about personal risks and specific research techniques involved with the study and, in fact, it could be argued that these types of study are minimal risk because of the stringent measures taken to ensure the ongoing confidentiality of data and samples (and the PMRP Ethics and Security Advisory Board did consider this project to be of minimal risk for that reason). It is unclear why the percentage of total responses correct and level of understanding in the PMRP was less than for NUgene. It could be due to differences in the education level, but data are not available to test this hypothesis. Another explanation for the observed differences could be education, training and/or experience of individuals presenting the information to the potential subjects, but again data are not available to evaluate this potential explanation.

Although small, it is still a concern that 2% of participants indicated that they felt pressured by study personnel and/or others to participate in PMRP. This bears further study, probably through focus groups or interviews that allow people to fully express themselves. Perceived coercion may be dependent upon the recruiters involved at the time of enrollment and that hypothesis could be explored through examining the percent of 'positive' responses by research coordinators. Further training and monitoring of the recruiting, consenting and enrolling process with research coordinators could then potentially decrease the percent of people who feel coerced by study staff.

Slightly more than one third of the study population felt that the USD 20 greatly influenced their decision to participate in the PMRP. A recently published study of hypothetical willingness to participate in a placebo-controlled clinical trial with varying levels of risk and payment found that increasing payment level does not alter perception of study risk and that wealthier people are more strongly influenced to participate by payment [8]. Because the payment amount for participation in the PMRP was chosen to cover time and expenses, it is understandable that subjects who live further outside Marshfield were more likely to have felt that the USD 20 payment greatly influenced their decision to participate; their cost to participate in terms of time and expense (gasoline to travel to Marshfield) was higher. Anecdotally, the percentage of people electing to return their USD 20 to the Marshfield Clinic Research Foundation has dropped over time as fuel prices have increased.

The major strength of this study is the size of the sample. The large sample allowed us to examine predictors of incorrect responses so that we could identify sub-groups of the population that would benefit from further information or a different approach to providing the information to make informed decisions about study participation. By using a previously validated tool, we were able to directly compare the results of our study to previous studies. Limitations of the current study result from the lack of information on household income or education levels that may explain, in part, comprehension of the informed consent information and the influence of payment on decision to participate.

In conclusion, the majority of study participants had a good level of understanding and knowledge of the purpose of the PMRP and did not feel undue coercion to participate. Future community consultation efforts that would accompany similar large scale population genetic studies should highlight the areas of lower comprehension, including the fact that individual results will not be returned to the participants, that many of the procedures are experimental, and that subjects' DNA will be stored for use indefinitely. These points were highlighted in the first newsletter to PMRP participants. In addition, Research Coordinators may need to take more time informing males and older individuals about project details so that they are making truly informed decisions about study participation.

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