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Consent for Genetic Research in the Framingham Heart Study

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Abstract

Extensive efforts have been aimed at understanding the genetic underpinnings of complex diseases that affect humans. Numerous genome-wide association studies have assessed the association of genes with human disease; including the Framingham Heart Study (FHS), which genotyped 550,000 SNPs in 9,000 participants. The success of such efforts requires high rates of consent by participants, which is dependent on ethical oversight, communications, and trust between research participants and investigators. To study this we calculated percentages of participants who consented to collection of DNA and to various uses of their genetic information in two FHS cohorts between 2002 and 2009. The data included rates of consent for providing a DNA sample, creating an immortalized cell line, conducting research on various genetic conditions including those that might be considered sensitive, and for notifying participants of clinically significant genetic findings were above 95%. Only with regard to granting permission to share DNA or genetic findings with for-profit companies was the consent rate below 95%. We concluded that the FHS has maintained high rates of retention and consent for genetic research that has provided the scientific freedom to establish collaborations and address a broad range of research questions. We speculate that our high rates of consent have been achieved by establishing frequent and open communications with participants that highlight extensive oversight procedures. Our approach to maintaining high consent rates via ethical oversight of genetic research and communication with study participants is summarized in this report and should be of help to other studies engaged in similar types of research.

Keywords

epidemiology; genetics; genome-wide association; medical ethics; population study

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INTRODUCTION

Since the beginning of the twentieth century, advances in the prevention and treatment of infectious diseases have led to a steady increase in childhood survival and in life expectancy. Today with people in developed and developing countries living longer, we have entered an era in which the greatest threats to global health are heart disease, cancer, stroke and other adult chronic diseases. Most of these diseases are believed to be the result of interactions between genetic factors and environmental exposures. Extensive efforts are underway to understand the genetic underpinnings of complex diseases that affect the lifespan and quality of life of humans. Marked advances in technology, however, have ushered in new challenges to the appropriate use of genetic science to promote improvements in public health.

Genome-wide association methods have been applied selectively to individual diseases. Numerous genome-wide association studies of 100,000 to 1,000,000 or more single nucleotide polymorphisms (SNPs) are now underway in a range of sample sizes from a few hundred to up to tens of thousands of people to assess the association of common genetic variants with human diseases. Numerous novel genetic associations have recently been reported for scores of traits and diseases, including some that hitherto were resistant to genetic discoveries (http://www.genome.gov/gwastudies/)

The Framingham Heart Study is a prospective epidemiology project that began recruiting participants in 1948 [Dawber et al, 1951]. In recent years, study investigators have collected DNA samples and have prepared immortalized cell lines -- to establish and maintain a renewable DNA resource -- in study participants from three generations within families. Because of its wealth of data, multigenerational structure, and extensive DNA resources, the Framingham Heart Study is an attractive research setting for genome-wide association studies (GWAS). The National Heart, Lung, and Blood Institute initiated a GWAS in the Framingham Heart Study. This new project, the SNP Health Association Resource (SHARe), genotyped approximately 550,000 SNPs in over 9,000 study participants (approximately 5 billion genotypes) (http://public.nhlbi.nih.gov/GeneticsGenomics/home/share.aspx). This detailed characterization of common human genetic variation across the entire genome has helped pinpoint common genetic signatures of disease and thereby identified new pathways related to health and disease [Levy et al, 2009, Köttgen et al, 2009, Dehghan et al, 2008]. The success of this effort is dependent on high rates of consent by study participation for collection of biosamples and for the conduct of genetic research. High rates of consent are closely linked to the implementation of procedures for ethical oversight of genetic research, informed consent, access to data by outside investigators and for-profit companies, protection of privacy and confidentiality, and participant notification of genetic results. Left unaddressed, participants' concerns about the oversight of genetic research could impact rates of participation in the study. Accordingly, for this investigation, we calculated the rates of participant consent from 2002–2009 to various uses of their DNA and genetic information.

MATERIALS AND METHODS

Description of the Framingham Heart Study

In 1948, the Framingham Heart Study, under the auspices of the US Public Health Service, embarked on a prospective population-based study [Dawber et al, 1951]. A central objective of the study was to identify factors that contribute to cardiovascular disease by following its development over a long period of time in a large group of community residents who were extensively evaluated. The researchers recruited an original cohort of 5209 men and women

between the ages of 28 and 62, including 1,644 spouse pairs, from the town of Framingham, Massachusetts, and began the first round of physical examinations, lifestyle interviews and laboratory tests that they would later analyze for common patterns related to cardiovascular disease development [Dawber et al, 1951]. Since 1948, the original cohort participants have continued to return to the study every two years for a detailed medical history, physical examination, and laboratory tests. In 1971 the study, with the formal involvement of Boston University, began the enrollment of a second-generation cohort consisting of 3548 children of the original cohort along with 1576 of their spouses[Feinleib, 1975]. Offspring cohort examinations were similar to those of the original cohort and were repeated approximately every four to eight years. Between 2002 and 2005, 4095 adults with at least one parent in the offspring cohort enrolled in the third generation cohort and underwent a clinic examination [Splansky, 2007]. The second examination of that cohort began in 2008.

Consent for Genetic Research

At the start of the clinic visit, study participants provide written informed consent as part of a process that is administered by clinic staff trained to answer questions and seek a senior investigator to address participant questions they cannot answer. For the initial visit of the third generation cohort (2002–2005), separate check boxes were created to obtain consent (or refusal) for DNA extraction and sharing of DNA and genetic data with researchers, cell line creation, and access to DNA and data by for-profit companies (http://www.framinghamheartstudy.org/research/pdfs/consent/gen3_exam1_consent.pdf). The consent process and the consent document have evolved in response to ongoing discussion with ethicists and study participants. Additional check boxes were included in the offspring cohort Examination 8 consent document (2005–2008) to determine participants' preferences for the use of their data for specific research areas, including some that might be viewed as sensitive or not part of the historic core mission of the Framingham Heart Study (e.g. reproductive health, mental health and alcohol use) (http://www.framinghamheartstudy.org/research/pdfs/consent/exam8_offsite_consent.pdf). The third generation cohort's second examination consent form (in use since 2008) similarly includes a check box regarding the conduct of studies of potentially sensitive areas of research, as described above (http://www.framinghamheartstudy.org/research/pdfs/consent/gen3_exam2_consent.pdf). In both cohorts, permission was also explicitly obtained to notify participants (and with their permission, a designated personal physician) about the results of genetic tests that have important health and treatment implications. The notification procedures are under development. Participant notification of genetic results will occur only when prespecified criteria are met: a genetic result has established analytic validity, the genetic variant poses significant and replicable risk for an important health condition, and proven therapeutic or preventive interventions exist for that condition [Bookman, 2006]. After initial consent is obtained to collect a cell line, the question was not repeated on subsequent consent forms. Similarly, when consent has been previously provided, questions are often removed from subsequent forms, in order to avoid unnecessary length and complexity.

For both cohorts, the right to withdraw from the study at any time is stated explicitly. It is important to note, however, that data sets have been created and distributed for public use (www.nhlbi.nih.gov/resources/deca/datasets_obv.htm). After they have been distributed we cannot go back and destroy data on participants who have withdrawn consent. We can only do so prospectively, by deleting their data from subsequent data sets. In addition, there has been continuous tracking of the level of permission for use of DNA samples and genetic research, especially protecting participants who have not been able to return for a recent examination. An annually updated database has been developed to track the most recent consent document provisions given by each participant as well as withdrawals of consent.

The informed consent documents were reviewed and approved by the Institutional Review Board of Boston University Medical Campus. Based on our most recently updated consent information, we have recorded the consent preferences for each of the consent provisions at each examination and calculated the percentage of participants who consented to each provision.

RESULTS

Preferences about Participation in Genetic Research

Tables I, II and III summarize the number (and percent) of offspring and third generation cohort participants who granted or refused permission for each of multiple informed consent preference fields. This analysis is based on 2980 offspring cohort participants, who attended their eighth clinic examination from 2005–2008, 4095 third generation cohort participants who attended their baseline clinic visit in 2002–2005, and 1141 third generation cohort participants who attended their second clinic examination, which began in 2008 and is ongoing. Data from the two third generation cohort examination cycles were analyzed separately due to slightly different consent forms. More than 99 percent of participants attending the examination affirmatively selected check boxes for participation in the clinical examination and genetic studies, extraction of DNA and sharing of DNA with researchers, creation of a cell line for generating renewable DNA resource, use of genetic information for other purposes, including research that might be regarded as sensitive, and notification of genetic findings with health implications that might be discovered as a result of research. A total of 240 offspring participants and 17 third generation participants (8.1% and 1.5% respectively) did not permit sharing their DNA or genetic data with private companies. Data from the first generation cohort was not obtained contemporaneously, so it was not analyzed for this study. However, they provided nearly universal approval at the last examination at which consent for DNA and genetic research were sought.

As of March 31, 2009 two individuals in the third generation cohort have withdrawn consent to participate in future clinic visits but maintained permission to use their previously collected data and DNA samples. Nine offspring cohort participants withdrew participation in further clinic examinations after examination cycle 7, which took place between 1998 and 2000. Two offspring participants withdrew consent to use their DNA. No offspring cohort participants have withdrawn after attending their eighth examination cycle 2005–2008).

DISCUSSION

This report found that more than 99 percent of offspring cohort participants at their eighth clinic visit and third generation cohort participants attending their first and second examination granted permission for DNA extraction and the creation of cell lines for genetic research. This is considerably higher than the 85 percent of participants in the National Health and Nutrition Examination Surveys who consented to genetic research in 2000[McQuillan et al, 2003]. In telephone interviews of 489 randomly selected people from Pennsylvania, 25 percent said they would not be willing to participate in medical research and 29 percent indicated uncertainty about participation[Trauth et al, 2000]. The Multiethnic Study of Atherosclerosis recently reported its rates of consent for genetic research and, in that study, full consent was granted by 79 percent of participants[Green et al, 2006]. The higher rates of consent for genetic research in Framingham Heart Study participants may be due in part to the nearly sixty year legacy of the program and the family-based design of the offspring and third generation cohorts. Before they arrived in clinic for their baseline examinations, eligible participants were aware of the history of the Framingham Heart Study from local media coverage and from their family members. The study's focus on familial patterns of disease and the genetic aims of the study were described in recruitment materials.

Thus, it is possible that eligible participants who strongly objected to genetic research declined study participation and their objections to consent for genetic research are not reflected in our data.

It is our belief, however, that our participants' high consent rates are also due in large part to our ongoing efforts to maintain communications with participants and to keep them informed about research activities and procedures including ethical oversight. We assert that the steps we have taken are vital to fostering the trust that is essential to maintain high rates of participation and retention in a prospective study. Beskow et al, conducted a survey that confirmed our proposed explanation for the Framingham Heart Study's high rates of consent and retention[Beskow et al, 2008]. It was determined through communication with potential research subjects that when investigators take steps to protect participants' privacy and confidentiality and keep them updated and informed, participants develop increasing trust for the research institution; these steps in turn favorably affect rates of consent.

The sole area with more than nominal unwillingness of Framingham participants to grant consent was for sharing of DNA and genetic data with private companies. Active restrictions to private sector access to data or DNA by Framingham Heart Study offspring cohort participants occurred in 2000–2001 when considerable publicity about a for-profit company's attempt to sell Framingham Heart Study data resulted in participant concerns about such efforts[Ready et al, 2001]. That private venture did not move forward, in large part because of inconsistency with informed consent provisions.

It is clear from our close interactions with participants that they enrolled in the Framingham Heart Study and continue to attend periodic clinic visits out of a strong desire to contribute to a scientific effort to improve public health. Sharing data and DNA with the outside research community is critical to maximizing the scientific knowledge gained from participation in the study. There remains inherent tension, however, between measures to maximize sharing of data and DNA with the outside research community to promote scientific discovery and restrictive measures to protect participants' privacy and confidentiality. Acknowledging this balance, we have developed procedures to achieve both aims, but recognize that they will evolve over time. Several of these procedures are described below. For example, we distribute datasets free of charge via the National Heart, Lung, and Blood Institute (http://www.nhlbi.nih.gov/resources/deca/directry.htm), and distribute genetic and phenotypic data at no charge via dbGAP (http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000007.v6.p3). Simultaneously, we protect privacy by removing identifiers, requiring IRB approval, and executed data distribution agreements for investigators requesting DNA and databases.

Despite the belief of some scientists and ethicists that identifiable DNA should not be used for any research purpose other than that specifically stated in the consent document[McGuire et al, 2006], such restrictions of scientific use would have a chilling effect on discovery, because many questions that can be addressed in the long term using banked specimens are not apparent at the time of study inception. Recently, Kaye, et al [2009] described the importance of data sharing in genomics and the challenges that researchers face in maintaining the highest ethical standards and participant/donor privacy when they share their data with other investigators. They provided several recommendations including specific oversight of data sharing by a committee *other than* an Institutional Review Board and accurate and complete consent forms that cover all possible uses of DNA at recipient institutions without overwhelming participants. Framingham has been taking steps towards these ends for several years.

In 2003 a panel of medical ethicists convened by the Framingham Heart Study recommended that the study establish an ethics advisory board to make recommendations on ethics issues as they arise, and that, "the board include study participants as well as local clergy, physicians, genetic counselors and an ethicist." In response, we sent a newsletter to all study participants summarizing the panel recommendations and announcing plans to form an ethics advisory board with participant membership (http://www.framinghamheartstudy.org/participants/newsletters/spring2004.pdf). In early 2004 the Framingham Heart Study Executive Committee established the Framingham Ethics Advisory Board, chaired by a medical ethicist (GK), and comprised of a genetic counselor, two attorneys, two physicians and a clergyman from the community, as well as several Framingham Heart Study participants representing each of the study cohorts. The Board has met approximately four times per year and the Framingham Heart Study has published its recommendations in newsletters sent to participants. Our approach is consistent with that of the Marshfield Clinic Personalized Medicine Research Project, which initiated conversations with participant focus groups, and formed an advisory board to improve communication and dialogue with study participants [McCarty, et al, 2008].

The topic of large-scale genetics research studies, including a genome-wide association study, was discussed at several Ethics Advisory Board meetings. Participants have been regularly informed via newsletters about the rationale for and conduct of a number of genetic research projects. In November 2005, as more details about a potential genome-wide association study became known, the Ethics Advisory Board expressed its approval in concept for such a project and recommended convening a focus group of study participants to review the study aims and obtain feedback. Such a meeting was held in December 2005 and a list of general questions was generated by the study participants (Supplemental material see online). These were assembled with answers and included in the February 2006 newsletter to all study participants along with a general article about genome-wide association studies (http://www.framinghamheartstudy.org/participants/newsletters/winter2006.pdf). The questions raised by participants related to communicating study plans, protections of privacy and confidentiality, informing participants about genetic results, withdrawal of consent, sharing data with the scientific community, and commercial access to data and DNA. Timed to coincide with a national press release (http://www.nhlbi.nih.gov/new/press/06-02-06.htm), the February 2006 Framingham Heart Study newsletter also included a letter from the director of the National Heart, Lung, and Blood Institute describing plans to pursue a genome-wide association study in the three Framingham Heart Study cohorts in a manner consistent with participants' preferences. In addition, Framingham staff received educational sessions on the same topics.

Already in existence at this time was a system by which Framingham Heart Study participants' DNA and genetic or non-genetic data are distributed free of charge to outside investigators with several safeguards to protect privacy and confidentiality: 1) the investigator must submit and receive approval of a DNA application (http://www.framinghamheartstudy.org/univapp/index.php), which is reviewed by a DNA Committee composed of four members including a chairperson with no scientific relation to the Framingham Heart Study, 2) the investigator must obtain project approval from the applicant's Institutional Review Board and, 3) the investigator and host institution must execute a Data and Materials Distribution Agreement (http://www.framinghamheartstudy.org/research/proposal.html) with the National Heart, Lung, and Blood Institute and Boston University. The distribution agreement prohibits investigators from redistributing data or DNA to any third party and it prohibits any attempt to identify participants. After these three conditions are met, DNA and data are distributed to the investigator with a new and unique set of random identifiers. Although DNA for

distribution is stripped of participants name and other identifying information (to prevent outright identification), it is not completely 'de-identified.' In other words, it is theoretically possible for participants to be linked to their DNA, but attempting to do so violates the Distribution Agreement.

Similarly, once genome-wide association study planning was underway, we began to develop a set of procedures to provide broad data sharing while maintaining the security of participant data. To address these needs, we deposited our genotype and phenotype data in dbGaP, a secure online data-sharing repository that grants investigators access to genotype and phenotype data with various safeguards (http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000007.v1.p1). In order to protect the confidentiality and privacy of participant data that are stored in dbGaP a Data Access Committee (DAC) was formed. In order to access genetic and phenotypic data, investigators must submit a Data Use Certification (DUC) application, in which they agree to abide by dbGaP rules not to share participants' information with third parties or make any attempt to identify participants. This application is then reviewed by the DAC, which reserves the right to terminate access upon breach of dbGaP policy. Institutional Review Board approval from the investigators' institution is also required for access to Framingham dbGaP data.

From our discussions with Framingham Heart Study participants about genetic research, we have learned that key among their concerns are a) the need for protections of privacy and confidentiality, b) a desire that data and biological specimens be shared at no cost with the scientific community to maximize discoveries and improve public health, and c) a need to honor restrictions of access to DNA and data by for-profit companies. These concerns, however, are likely to be universal and not exclusive to the Framingham Heart Study. Similar concerns about genetic research emerged in the deCODE genetics study in Iceland, including opposition by the Icelandic Medical Association[Annas et al, 2000]. Icelandic dissent centered on protections of privacy, for-profit use of DNA and data, lack of voluntary participation, restricted access to the data by the scientific community and inclusion of medical records in a for-profit database without specific individual consent. In addition, similar concerns were expressed by residents of British Columbia participating in a study of the public's attitudes towards informed consent in genetic research. Participants were most concerned with balancing their own confidentiality and privacy with ensuring that their DNA and data be available for useful research to promote the public good [Secko et al, 2009]

Whereas characterization of genetic variation across the human genome is now technically feasible and in widespread use, large-scale genetic studies must be carried out in a manner consistent with the preferences expressed by study participants in the informed consent process. This report describes the procedures implemented for ethical oversight of genetic research in the Framingham Heart Study, including the informed consent process, access to data by outside investigators and for-profit companies, and protections of privacy and confidentiality. We are engaged in ongoing communications with study participants to inform them about the goals of our genetic research program and seek their comments and concerns. Importantly, we established an Ethics Advisory Board that includes Framingham Heart Study participants to review genetic research and ensure its consistency with their consent and their wishes.

Moreover, given the myriad of questions that can be addressed via genetic studies, the Framingham Heart Study specifies multiple general areas of use in our current informed consent document (Table 1, 2, 3), while not specifying hundreds of potential areas of scientific inquiry. This practice educates our participants about the potential areas of

research without overwhelming them with each and every conceivable possibility. Caulfield et al recommended that whenever genome-wide association studies are conducted, participants should have the ability to withdraw consent at any time should they change their mind[Caulfield et al, 2008]. The Framingham Heart Study has consistently notified participants of their right to withdraw consent for future distribution of any sample they have donated and has made a concerted effort to keep each participant's consent information up to date. The number of withdrawals of consent among Framingham Heart Study participants has been very low.

The Framingham Heart Study has succeeded in obtaining high rates of consent for genetic research and has taken multiple steps outlined above to implement ethical oversight of the large-scale genetic research that it is currently conducting. Lessons from the Framingham experience described in this report should be considered by other studies engaged in human subjects' research to assist in the development of procedures to ensure ethical oversight of genetic research in a manner consistent with participants' preferences. By developing detailed consent procedures and the ability to track decisions, means for communicating study plans with participants, and participant involvement in ethical oversight of genetic research, we have been able to maximize rates of participation in and consent for research, and we are hopeful that this pattern will be continued in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I

Consent for Various Uses of DNA and Data in the Offspring Cohort (2005–2008)

Check Box	Answer	Participants Consented (%)
I agree to participate in the Framingham Heart Study examinations described above to study the frequency of and factors contributing to heart and blood vessel diseases, lung and blood diseases, stroke, memory loss, and other diseases and health conditions.	Yes	2980 (100)
	No	0 (0)
I agree to provide a blood sample from which DNA and other components can be extracted. The DNA will be made available to researchers studying the diseases listed above.	Yes	2891 (99.9)
	No	3 (0.1)
If a cell line has not already been collected, I agree to allow a cell line to be made from a sample of my blood to provide a renewable supply of DNA. (A cell line is a frozen sample of specially processed white cells from your blood that allows us to grow more white cells and get more DNA from them in the future as needed for research projects).	Yes	2969 (99.7)
	No	10 (0.3)
I agree to participate in the genetic studies of factors contributing to heart and blood vessel diseases, lung and blood diseases, stroke, and memory loss.	Yes	2978 (99.9)
	No	2 (0.1)
I agree to participate in genetic studies of other diseases and health conditions including but not limited to joint disease, bone loss, and cancer.	Yes	2974 (99.8)
	No	5 (0.2)
I agree to participate in genetic studies of reproductive conditions and mental health conditions such as alcohol use and depressive symptoms.	Yes	2970 (99.7)
	No	10 (0.3)
I agree to allow researchers from private companies to have access to my DNA and genetic data which may be used to develop diagnostic lab tests or pharmaceutical therapies that could benefit many people. (Note: You or your heirs will not benefit financially from this, nor will your DNA be sold to anyone.)	Yes	2739 (91.9)
	No	240 (8.1)
If a genetic condition is identified that may have potentially important health and treatment implications for me, I agree to allow the Framingham Heart Study to notify me and with my permission to notify my physician.	Yes	2964 (99.5)
	No	16 (0.5)

Table II

Consent for Various Uses of DNA and Data in the Third Generation Cohort Exam 1 (2005–2008)

Check Box	Answer	Participants Consented (%)
I agree to participate in the physical examination and genetic studies of factors contributing to heart and blood vessel diseases, lung and blood diseases, stroke, memory loss, joint disease, bone loss, deafness, cancer, and other major diseases and health conditions.	Yes	4095 (100)
	No	0 (0)
I agree to provide a blood sample from which DNA and other components can be extracted. The DNA will be made available to researchers studying the diseases listed above.	Yes	4092 (99.9)
	No	3 (0.1)
I agree to allow the creation of a cell line from my blood sample to provide a renewable supply of DNA. (A cell line is a frozen sample of specially processed white cells from your blood that allows us to grow more white cells and get more DNA from them in the future as needed for research projects.)	Yes	4082 (99.7)
	No	12 (0.3)
I agree to allow researchers from private companies to have access to my DNA and genetic data which may be used to develop diagnostic lab tests or pharmaceutical therapies that could benefit many people. (Note: You or your heirs will not benefit financially from this, nor will your DNA be sold to anyone.)	Yes	4000 (98.0)
	No	95 (2.0)

** Remaining 3584 are indeterminate if check box was left blank; question was not on paper consent for or question was not on early data entry screen

Table III

Consent for Various Uses of DNA and Data in the Third Generation Cohort Exam 2 (2008–2010)*

Check Box	Answer	Participants Consented (%)
I agree to participate in the FHS clinic examination and studies of the factors contributing to heart and blood vessel diseases, lung and blood diseases, stroke, memory loss, cancer, and other major diseases and health conditions.	Yes	1141 (100)
	No	0 (0)
I agree to provide a blood sample from which genetic material (DNA and other components) can be obtained. I agree to allow my data and blood samples to be used in the genetic studies of factors contributing to heart and blood vessel diseases, lung and blood diseases, stroke, memory loss, cancer, and other diseases and health conditions.	Yes	1140 (99.9)
	No	1 (0.1)
I agree to allow my data and blood samples to be used in genetic studies of reproductive conditions, and mental health conditions such as alcohol use and depressive symptoms.	Yes	1141 (100)
	No	0 (0)
I agree to allow researchers from commercial companies to have access to my DNA and genetic data which may be used to develop new lab tests or treatments that could benefit many people. (You or your heirs will not benefit financially from this, nor will your DNA be sold to anyone.)	Yes	1123 (98.5)
	No	17 (1.5)
If a genetic condition is identified that may have important health and treatment implications for me, I agree to allow the FHS to notify me, and then with my permission to notify my physician.	Yes	1134 (100)
	No	0 (0)

* Exam cycle is still underway