

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

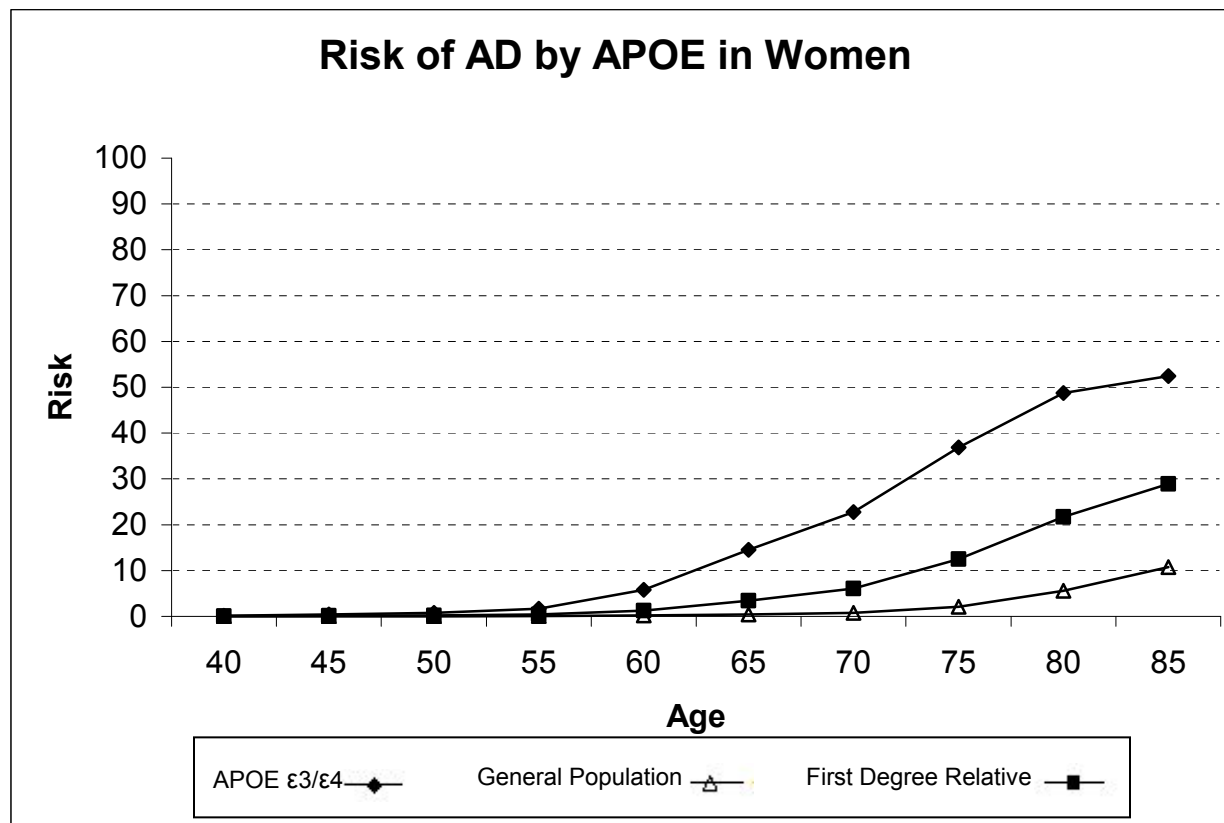
Supplement to: Green RC, Roberts JS, Cupples LA, et al. Disclosure of APOE genotype for risk of Alzheimer's disease. *N Engl J Med* 2009;361:xxxx-xx.

SUPPLEMENTAL FIGURES

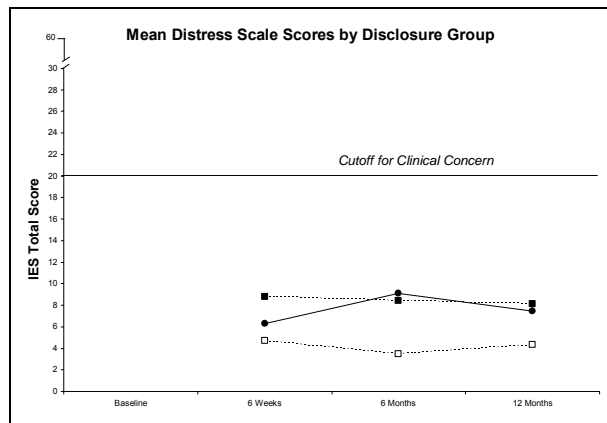
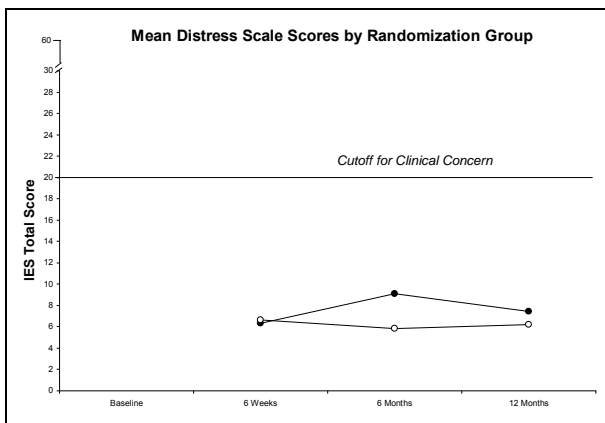
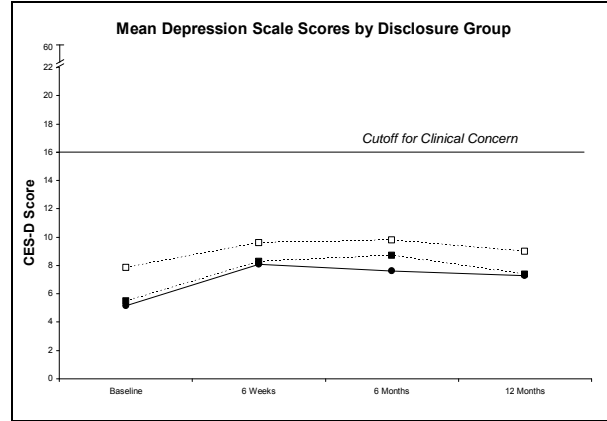
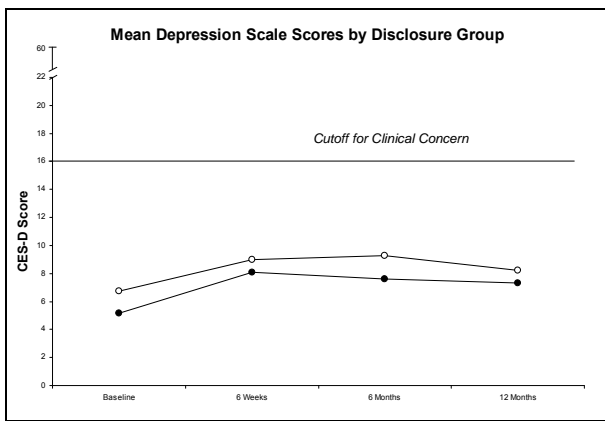
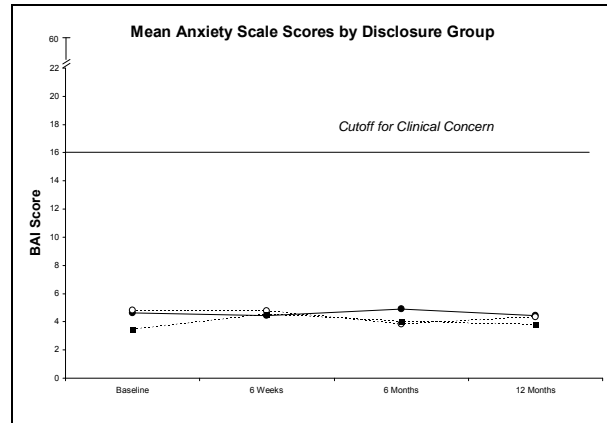
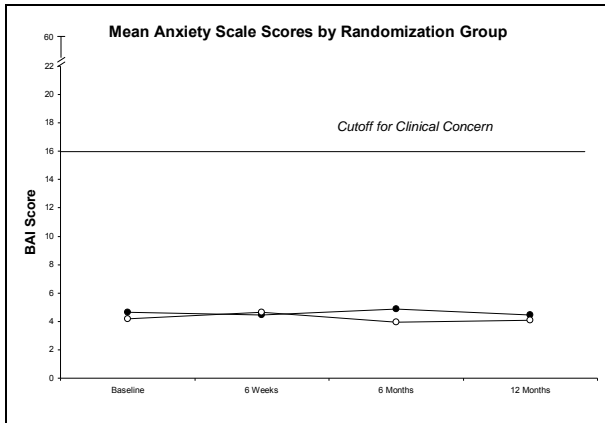
Supplemental Table 1. Responses at 6 weeks to questions about risk perception, overall impact and potential regret at finding out the information

Score Type	GND (N=51)	GDε4- (N=58)	GDε4+ (N=53)
Risk Perception in comparison to pre-disclosure...			
Chances of getting AD seem higher	2.3%	1.8%	34.7%
Chances of getting AD seem the same	70.4%	23.6%	53.1%
Chances of getting AD seem lower	27.3%	74.6%	12.2%
Overall Impact of receiving risk information...			
Positive Impact	42.2%	85.4%	45.8%
Neutral Impact	51.1%	12.7%	18.8%
Negative Impact	6.8%	1.8%	35.4%
Knowing what you now know, would you choose to do it again...			
Yes	90.5%	98.2%	98.0%
No	9.5%	1.8%	2.0%

Supplemental Figure 1: Example of cumulative incidence lifetime risk curves shown to participants in the intervention (disclosure) group, in this case to women with the $\epsilon 3/\epsilon 4$ genotype

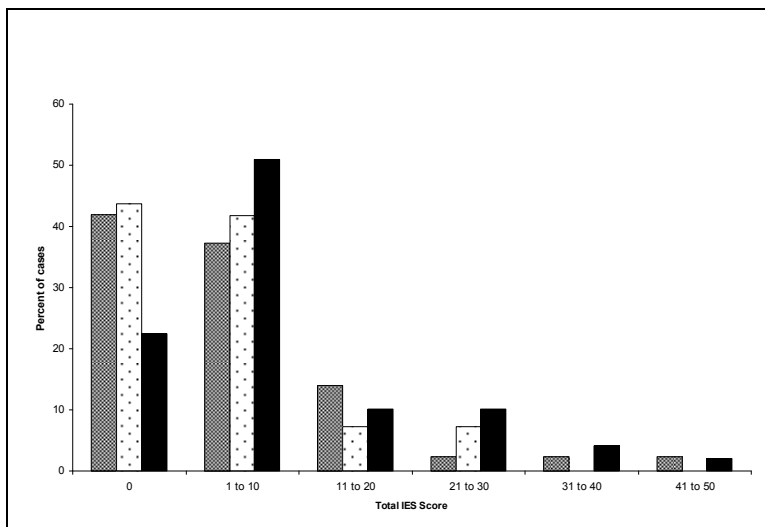
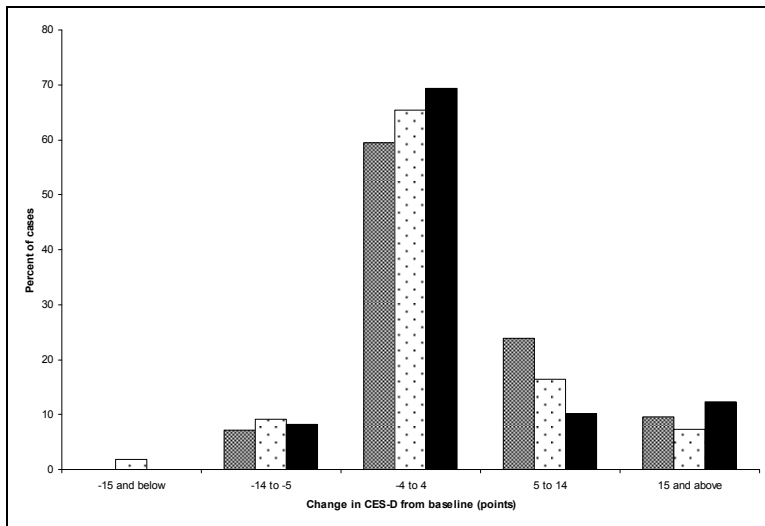
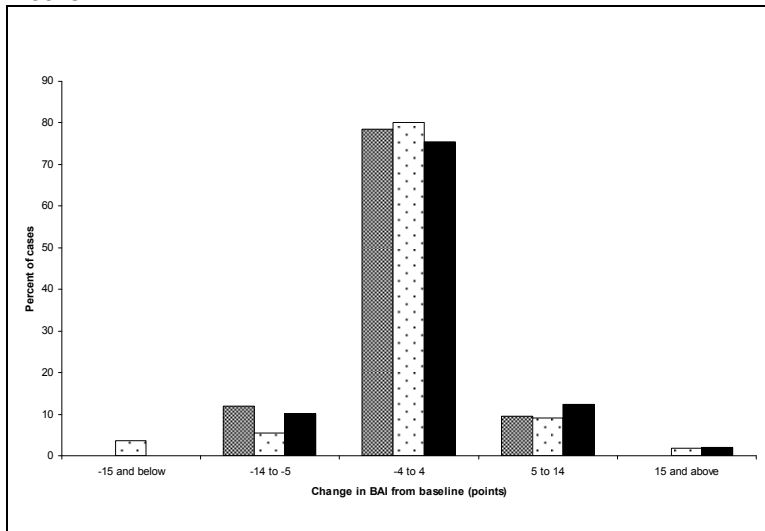


Supplemental Figure 2. Unadjusted Mean Scores of BAI, CES-D and IES by Study Group



- GND
- GD
- - □ - - GDe4-
- - ■ - - GDe4+

Suppl Fig. 3. Individual Changes on Anxiety, Mood and Distress Scale Scores by Disclosure Group at 6 Weeks



■ GND
 □ GDe4-
 ■ GDe4+



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Informed Consent

“Genetic Risk Assessment and Counseling for Alzheimer’s Disease” Step I

(Consent to be obtained in person, by telephone or by mail from the proxy (primary family caregiver) for living or deceased persons with probable or autopsy confirmed Alzheimer’s disease, hereafter referred to as Alzheimer’s disease)

INTRODUCTION AND PURPOSE

You are being asked to participate in a research study that will explore the attitudes and decisions of family members of persons with Alzheimer’s disease who are offered genetic risk assessment for the disease. Genetic risk assessment is determined by family history and analysis of susceptibility genes from a blood sample. This information will allow researchers to determine susceptibility to Alzheimer’s disease. Susceptibility to Alzheimer’s disease is important because for more than 95% of families, no one gene has been identified that causes Alzheimer’s disease or can determine if a specific unaffected individual will develop the disease in the future. Obtaining risk information of Alzheimer’s disease will hopefully be beneficial in the future if treatments are identified that will slow or prevent the progress of the disease.

You will be asked questions about your age, gender, education and employment history. You will also be asked similar questions as well as medical history questions about _____, your spouse or relative who has or had Alzheimer’s disease. It will take approximately 20-30 minutes to answer the questions. You will be asked permission to contact the adult son or daughter of the individual in your family with Alzheimer’s disease. Adult children will be invited to participate in the next phase of the study where they will be asked some questions about their attitudes toward genetic testing and counseling and offered the opportunity to enter the next phase of the study where genetic risk assessment will be provided. A separate consent form will be used for the next step of the study.

NUMBER OF PERSONS EXPECTED TO PARTICIPATE IN THE STUDY

Approximately 300 proxies (primary family caregivers) of persons with Alzheimer’s disease will be enrolled in this study at three sites in the United States (Boston, Cleveland and New York). Approximately 100 will be enrolled at this study site.

RISKS

There are no risks to you in answering these questions, although some questions are personal and may make you uncomfortable. You have the right to refuse to answer these questions now, or to stop at any time.

BENEFITS

There are no specific benefits to you from participating in this study. However, your participation in this study may contribute to a better understanding of attitudes and decisions of people who are offered genetic risk assessment for Alzheimer's disease.

DISCOMFORT OR INJURY

If participating in this study causes you to have some anxiety about the risk of your family members for developing Alzheimer's disease or any other discomfort, you can call the study's principal investigator, Dr. Robert C. Green at (617) 638-5393 who will provide the appropriate assistance for you.

At this time there is no way of determining with certainty if an individual will develop Alzheimer's disease.

CONFIDENTIALITY

A Certificate of Confidentiality has been obtained from the Department of Health and Human Services for this study to help insure your privacy. This certificate means that the researchers cannot be forced to tell people who are not connected with the study, including courts, about your participation, without your written consent. If we learn something that would immediately danger you or others, we may discuss it with you, if possible, or seek help. The Institutional Review Board of Boston University Medical Center and the United States Food and Drug Administration may examine your study records. All information obtained from this study will be locked and stored in a way to ensure confidentiality. No information about you or your family members will be released without your written permission. You will not be identified by name in any publication resulting from this study.

QUESTIONS OR PROBLEMS

You are encouraged to ask questions about the study and your rights as a participant. You may contact Dr. Robert C. Green at (617) 638-5393 for answers to questions about this study or any discomforts that arise from your participation.

If you have questions about your rights as a research subject, you may contact the Office of the Institutional Review Board for Human Research of Boston University Medical Center at (617) 638-7207.

RIGHT TO REFUSE OR WITHDRAW

Your participation in this study is completely voluntary and if you do decide to participate you may stop at any time simply by telling one of the investigators. As an alternative to participating in this study, you may choose not to partake in this research and not to pursue risk assessment for Alzheimer disease. No penalty or loss of benefits to which you or the person with Alzheimer disease are entitled will occur if you decide not to participate. Even if you decide to participate now, you may stop or withdraw at any time without prejudice. You and the person with Alzheimer disease will not be penalized in any way.

COMPENSATION

No monetary compensation will be provided for participation in this study.

ALTERNATIVES

The alternative to this study is not to participate.

PROXY'S STATEMENT OF CONSENT

You have been asked to grant consent for participation of your _____ in this study, on his/her behalf. In the judgment of the physician caring for _____, she/he is unable to adequately understand the informed consent form, due to severity of illness, and/or the effects of medications and/or is otherwise unable to sign the form (e.g. is now deceased).

I have read this informed consent form and the above paragraph. The decision to grant consent for this study is that which I believe the patient would have made were she/he able to make such a decision. I have been informed of the risks and benefits involved, and all of my questions have been answered to my satisfaction. I have been assured that any future questions will also be answered by a member of the research team. I will receive a signed copy of this form.

In the event injury occurs resulting from research procedures, medical treatment will be available at Boston Medical Center. However, no special arrangements for compensation or for payment will be made by Boston Medical Center, solely because of my participation in this experiment. This is a policy statement of Boston Medical Center and Boston University, and does not waive any of my legal rights.

I am free to withdraw this consent and discontinue participation in this study at any time without prejudice to myself or the patient with Alzheimer disease.

I hereby give consent for _____ to participate in this research.

Date

Proxy's Signature

Proxy's Printed Name

I have explained this project to the caregiver, and I am available to answer any questions now, or in the future.

Date

Physician/Co-Investigator's Signature

Physician/Co-investigator's Printed Name

Informed Consent

“Genetic Risk Assessment and Counseling for Alzheimer’s Disease” Step II

(Consent to be obtained in person, by telephone or by mail from the adult offspring of living or deceased persons with probable or autopsy confirmed Alzheimer’s disease, hereafter referred to as Alzheimer’s disease)

INTRODUCTION AND PURPOSE

Your name was provided to us by _____ so that we could ask you to participate in the second phase of a study to explore the attitudes and decisions of people toward genetic risk assessment for Alzheimer’s disease.

You are being asked to participate in a research study that will explore the attitudes and decisions of family members of persons with Alzheimer’s disease who are offered genetic risk assessment for the disease. Genetic risk assessment is determined by family history and analysis of susceptibility genes from a blood sample. This information will allow researchers to determine susceptibility to Alzheimer’s disease. Susceptibility to Alzheimer’s disease is important because in more than 95% of families, no one gene has been identified that causes Alzheimer’s disease or can determine if a specific unaffected individual will develop the disease in the future. Obtaining risk information of Alzheimer’s disease will hopefully be beneficial in the future if treatments are identified that will slow or prevent the degenerative process of the disease.

You are being asked to participate in an educational session to learn more about Alzheimer’s disease, and an initial meeting with a genetic counselor to discuss your family history of Alzheimer’s disease and to undergo neuropsychological screening tests to evaluate depression, thinking, mood and memory. If any abnormality is found on these tests, you will not be eligible to participate in the study and will be referred for appropriate clinical evaluation. Otherwise, you will be invited to participate in the final step of the study, where you would be offered risk assessment and counseling. If you agree to participate in the next phase of this study, you will be asked to read and sign another consent form detailing information about your further participation.

NUMBER OF PERSONS EXPECTED TO PARTICIPATE IN THE STUDY

Approximately 300 adult sons and daughters of persons with Alzheimer’s disease will be enrolled in this study at three sites in the United States with approximately 100 enrolled at this study site.

RISKS

Risks from participation in this study include the invasion of privacy from the review of medical records, discomfort or fatigue associated with answering questions and neuropsychological testing and finding out that you have a cognitive impairment or psychological condition. You have the right to refuse to participate now, or to stop at any time.

This study will focus only on Alzheimer’s disease. The session with the genetic counselor is not designed to identify conditions other than Alzheimer’s disease. However, if in the course of meeting with the genetic counselor it is incidentally discovered that another genetic concern may exist in your family, you will be given the option to be referred to another genetics professional. This will not interfere with your participation in this study unless the Alzheimer’s disease in your family appears to be caused by a rare single gene.

BENEFITS

There are no specific benefits to you from participating in this study. However, your participation in this study may contribute to a better understanding of attitudes and behaviors of people who are offered genetic risk assessment for Alzheimer's disease.

DISCOMFORT OR INJURY

If participating in this study causes you to have some anxiety about the risk of your family members for developing Alzheimer's disease or any other discomfort, you can call the study's principal investigator, Dr. Robert C. Green at (617) 638-5393 who will provide the appropriate assistance for you.

At this time there is no way of determining with certainty if an individual will develop Alzheimer's disease.

CONFIDENTIALITY

A Certificate of Confidentiality has been obtained from the Department of Health and Human Services for this study to help insure your privacy. This certificate means that the researchers cannot be forced to tell people who are not connected with the study, including courts, about your participation, without your written consent. If we learn something that would immediately danger you or others, we may discuss it with you, if possible, or seek help. The Institutional Review Board at Boston University Medical Center and the United States Food and Drug Administration may examine your study records. All information obtained from this study will be locked and stored in a way to ensure confidentiality. No information about you or your family members will be released without your written permission. You will not be identified by name in any publication resulting from this study.

QUESTIONS OR PROBLEMS

You are encouraged to ask questions about the study and your rights as a participant. You may contact Dr. Robert C. Green at (617) 638-5393 for answers to questions about this study or any discomforts that arise from your participation.

If you have questions about your rights as a research subject, you may contact the Office of the Institutional Review Board for Human Research of Boston University Medical Center at (617) 638-7207.

RIGHT TO REFUSE OR WITHDRAW

Your participation in this study is completely voluntary and if you do decide to participate you may stop at any time, simply by telling one of the investigators. As an alternative to participating in this study, you may choose not to partake in this research and not to pursue risk assessment for Alzheimer disease. No penalty or loss of benefits to which you or the person with Alzheimer's disease are entitled will occur if you decide not to participate. Even if you decide to participate now, you may stop or withdraw at any time without prejudice. You and the person with Alzheimer's disease will not be penalized in any way.

COMPENSATION

No monetary compensation for participation in this study will be provided.

ALTERNATIVES

The alternative to this study is not to participate.

SUBJECT'S STATEMENT OF CONSENT

I have read the above description of this research study, and I understand it. I have been informed of the risks and benefits involved, and all of my questions have been answered to my satisfaction. I have been assured that any future questions will also be answered by a member of the research team. I will receive a copy of this form.

In the event injury occurs resulting from research procedures, medical treatment will be available at Boston Medical Center. However, no special arrangements for compensation or for payment will be made by Boston Medical Center, solely because of my participation in this experiment. This is a policy statement of Boston Medical Center and Boston University, and does not waive any of my legal rights.

I am free to withdraw this consent and discontinue participation in this study at any time without prejudice to myself or my relative with Alzheimer's disease.

I voluntarily consent to participate in the described research study.

Date

Subject's Signature

Subject's Printed Name

I have explained this project to the subject, and I am available to answer any questions now, or in the future.

Date

Physician/Co-Investigator's Signature

Physician/Co-investigator's Printed Name



IRB Protocol # 2000-25
Robert C. Green, MD
Tamsen Brown, MS

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Informed Consent

“Genetic Risk Assessment and Counseling for Alzheimer’s Disease” Step III

Primary Study Participant

(Consent to be obtained in person from the adult offspring of living or deceased persons with probable or autopsy confirmed Alzheimer’s disease, hereafter referred to as Alzheimer’s disease)

INTRODUCTION AND PURPOSE

You are invited to participate in a research study of Genetic Risk Assessment and Counseling for Alzheimer’s disease at the Boston University School of Medicine. Genetic risk assessment will be determined by analyzing both family history and genes from a blood sample. This study will attempt to learn the role of genetic testing and counseling in the management of Alzheimer’s disease and the consequences of learning risk information based on genetic testing. You were selected as a possible participant in this study because you are the son or daughter of an individual diagnosed with Alzheimer’s disease. If you decide to participate, you will review the option of genetic testing with a genetic counselor. We will then draw 1-2 tablespoons of blood for the purpose of analyzing your genetic material known as DNA. The DNA analysis will look at the apolipoprotein E gene (APOE). A certain form of this gene has been found to be associated with an increased risk of Alzheimer’s disease. The results from your DNA analysis can be used to estimate your future risk of developing Alzheimer’s disease. However, a risk estimate is not exact, and other genes and factors may alter your actual risk of developing the disease.

After the blood draw, you will be randomly placed (like the flip of a coin) into one of two study groups. The first study group will receive a risk assessment based on family history and genetic testing results. The second group will receive risk assessment based on family history alone and will not receive genetic test results during the course of this study. When you return for the 1-hour genetic counseling session in which results and risk assessment of developing Alzheimer’s disease are disclosed, you will learn which group you are in. We will schedule you for follow-up appointments at 6 weeks and 6 months after disclosure of results. During each of these 30-60 minute appointments, you will again undergo the neuropsychological tests and mood scales introduced at the initial session in the previous step of this study. We will also ask you a series of questions concerning any impact this study may have had on your attitudes and future plans. For this portion of the study, there will be a total number of 3 visits over the course of 6 months. In addition, we will make follow-up phone calls to you 1 week, 8 months and 12 months after disclosure of results.

NUMBER OF PERSONS EXPECTED TO PARTICIPATE IN THE STUDY

Approximately 300 adult sons and daughters of persons with Alzheimer’s disease will be enrolled in this study at three sites in the United States with approximately 100 enrolled at this study site.

BLOOD SAMPLE HANDLING

Any genetic material left over from the blood specimen will be frozen and stored for 15 years after the study is over. You may indicate on the last page whether you wish to authorize us to use your blood sample for confidential research on Alzheimer's disease. If we wish to use the frozen blood sample in the future for other studies, we will contact you to ask you for your permission. Your blood sample will not be used for any other purpose without your written consent. We will not create a cell line from your stored blood sample. Specifically, we will not use the sample to test for any medical illness or genetic disorder (other than Alzheimer's disease) nor will it be sold or used for commercial purpose.

Aside from APOE genotype information, you will not be informed about any other genetic markers that are investigated on your blood sample. However, if we identify clinically significant information on your banked blood sample, we will make every effort to contact you in writing, and appropriate referrals to clinical specialists will be made if possible.

RISKS

Possible risks from participation in the study include minor bruising or pain from the blood draw, the invasion of privacy from the review of medical records, and discomfort or fatigue associated with neuropsychological testing. After learning the results of the genetic test, there is a possible risk of psychological harm such as worry and anxiety. There is a possible risk of adverse effects on your future employability, insurability and family/social relations if results of the test are disclosed. Even though we will not disclose your test results to any third party without your written consent, and neither practitioners nor insurance companies currently ask for such information, it is possible that your insurance company could ask you for information related to your genetic testing and/or results. We have taken steps to protect subjects from the risks of this study (see "Confidentiality" section). Additional support and counseling will always be readily available if you experience anxiety or any other adverse reactions. If you need long term counseling, we will make the appropriate referral. However, you or a third party payer will be responsible for the cost of counseling.

BENEFITS

Although we cannot guarantee that you will receive any benefits from participation in this study, the results of this study may be of benefit to Alzheimer's patients and their families in the future if genetic testing proves useful in the management of the disease. If new information becomes available on genetic risk information during the course of the study, we will make every effort to inform you.

RIGHT TO REFUSE OR WITHDRAW

Your participation in this study is completely voluntary and if you do decide to participate you may stop at any time simply by telling one of the investigators. As an alternative to participating in this study, you may choose not to partake in this research and not to pursue risk assessment for Alzheimer disease. You may request that your blood sample be stripped of all identifiers and/or destroyed at any time. You will not be penalized in any way if you decide not to participate or decide to withdraw. No penalty or loss of benefits to which you are entitled will occur if you decide not to participate. Your decision as to whether to participate will not prejudice your or your AD-affected parent's future relations or with Boston University School of Medicine. If you elect not to participate in this study, you may still be eligible for other future studies at this or any other center.

CONFIDENTIALITY

A Certificate of Confidentiality has been obtained from the Department of Health and Human Services for this study to help insure your privacy. This certificate means that the researchers cannot be forced to tell people who are not connected with the study, including courts, about your participation, without your written consent. If we learn something that would immediately danger you or others, we may discuss it with you, if possible, or seek help. If we feel at any time that your welfare is in danger, we reserve the right to terminate your participation in this study. All information obtained from this study and identified with you will remain confidential and will be disclosed only with your permission. We will not disclose the results to your physician, insurance company or family members unless you specifically ask us to do so. All blood samples will be coded with a number and only our researchers will be able to identify you as the source of the sample. Information will be stored in a protected computer database. However, the National Institute of Health, United States Food and Drug Administration and the Institutional Review Board at Boston University may have access to data from this study. Dr. Norman Relkin at Cornell University and Dr. Peter Whitehouse at Case Western Reserve University also will have access to information obtained during the course of the study because they are collaborating investigators. If any of your information is used for publication, you and your family members will not be identifiable in any way.

COSTS/COMPENSATION

You will not be responsible for any costs of counseling or testing that you will receive for the duration of your participation in this study. Transportation costs to and from the hospital will be paid up to \$30 per visit.

DISCOMFORT OR INJURY

If participating in this study causes you to have some anxiety about the risk of your family members for developing Alzheimer's disease or any other discomfort, you can call the study's principal investigator, Dr. Robert C. Green at (617) 638-5355 who will provide the appropriate assistance for you.

At this time there is no way of determining with certainty if an individual will develop Alzheimer's disease.

QUESTIONS OR PROBLEMS

You are encouraged to ask questions about the study and your rights as a participant. You may contact Dr. Robert C. Green at (617) 638-5355 for answers to questions about this study or any discomforts that arise from your participation. If you have questions about your rights as a research subject, you may contact the Office of the Institutional Review Board for Human Research of Boston University Medical Center at (617) 638-7207.

ALTERNATIVES

The alternative to this study is not to participate.

SUBJECT'S STATEMENT OF CONSENT

I have read the above description of this research study. I have been informed of the risks and benefits involved, and all of my questions have been answered to my satisfaction. I have been assured that any future questions will also be answered by a member of the research team. I will receive a signed copy of this form.

In the event injury occurs resulting from research procedures, medical treatment will be available at Boston Medical Center. However, no special arrangements for compensation or for payment will be made by Boston Medical Center, solely because of my participation in this experiment. This is a policy statement of Boston Medical Center and Boston University, and does not waive any of my legal rights.

I am free to withdraw this consent and discontinue participation in this study at any time without prejudice.

I voluntarily consent to participate in the described research study and wish for my DNA to be stored for this purpose.

___ I do wish for my DNA to be used **confidentially** for future research on aging and Alzheimer's disease.

___ I do not wish for my DNA to be used for any research other than what is described for this research study.

Date

Subject's Signature

Subject's Printed Name

I have explained this project to the subject, and I am available to answer any questions now, or in the future.

Date

Physician/Co-Investigator's Signature

Physician/Co-investigator's Printed Name