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Featured Article

Alzheimer's Prevention Initiative Generation Program: Development of an *APOE* genetic counseling and disclosure process in the context of clinical trials

Carolyn M. Langlois[a], Angela Bradbury[b], Elisabeth M. Wood[b], J. Scott Roberts[c], Scott Y. H. Kim[d], Marie-Emmanuelle Riviere[e], Fonda Liu[f], Eric M. Reiman[a,g,h,i,j,k], Pierre N. Tariot[a], Jason Karlawish[l], Jessica B. Langbaum[a,*]

[a]*Banner Alzheimer's Institute, Phoenix, AZ, USA*
[b]*Department of Medical Ethics and Health Policy, University of Pennsylvania, Philadelphia, PA, USA*
[c]*Department of Health Behavior and Health Education, University of Michigan School of Public Health, Ann Arbor, MI, USA*
[d]*National Institutes of Health, Bethesda, MD, USA*
[e]*Novartis Pharma AG, Basel, Switzerland*
[f]*Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA*
[g]*Neurodegenerative Disease Research Center, Arizona State University, Tempe, AZ, USA*
[h]*Department of Psychiatry, University of Arizona School of Medicine – Phoenix, Phoenix, AZ, USA*
[i]*Department of Psychiatry, University of Arizona, Tucson, AZ, USA*
[j]*Neurogenomics Division, Translational Genomics Research Institute, Phoenix, AZ, USA*
[k]*Arizona Alzheimer's Consortium, Phoenix, AZ, USA*
[l]*Departments of Medicine, Medical Ethics and Health Policy, and Neurology, University of Pennsylvania, Philadelphia, PA, USA*

Abstract

Introduction: As the number of Alzheimer's disease (AD) prevention studies grows, many individuals will need to learn their genetic and/or biomarker risk for the disease to determine trial eligibility. An alternative to traditional models of genetic counseling and disclosure is needed to provide comprehensive standardized counseling and disclosure of apolipoprotein E (*APOE*) results efficiently, safely, and effectively in the context of AD prevention trials.

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*Corresponding author. Tel.: +1-602-839-2548; Fax: +1-602-839-6296.
E-mail address: jessica.langbaum@bannerhealth.com

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Methods: A multidisciplinary Genetic Testing, Counseling, and Disclosure Committee was established and charged with operationalizing the Alzheimer's Prevention Initiative (API) Genetic Counseling and Disclosure Process for use in the API Generation Program trials. The objective was to provide consistent information to research participants before and during the *APOE* counseling and disclosure session using standardized educational and session materials.
Results: The Genetic Testing, Counseling, and Disclosure Committee created a process consisting of eight components: requirements of *APOE* testing and reports, psychological readiness assessment, determination of AD risk estimates, guidance for identifying providers of disclosure, predisclosure education, *APOE* counseling and disclosure session materials, *APOE* counseling and disclosure session flow, and assessing *APOE* disclosure impact.
Discussion: The API Genetic Counseling and Disclosure Process provides a framework for large-scale disclosure of *APOE* genotype results to study participants and serves as a model for disclosure of biomarker results. The process provides education to participants about the meaning and implication(s) of their *APOE* results while also incorporating a comprehensive assessment of disclosure impact. Data assessing participant safety and psychological well-being before and after *APOE* disclosure are still being collected and will be presented in a future publication.

Keywords: Alzheimer's disease; *APOE*; Genetic counseling; Genetic disclosure; Alzheimer's Prevention Initiative; Generation Program; Clinical trials; Clinical research; Prevention

1. Introduction

Alzheimer's disease (AD) poses a tremendous medical, economic, and societal burden [1]. In response, the National Plan to Address Alzheimer's Disease has set an ambitious goal of developing treatments to delay onset of AD and related dementias by 2025 [2]. Given this heightened urgency, at least eight trials of preclinical AD (i.e., prevention) treatments have been attempted, are ongoing, or are in various stages of planning [3]. Unlike trials conducted in individuals in the symptomatic stages of AD, preclinical AD trials enroll cognitively healthy participants who are at increased risk for developing clinical symptoms of AD because of their age, genetics, or the presence of AD-related biomarkers. Trials that use genes or biomarkers as eligibility criteria therefore typically require participants to learn sensitive information along with the associated implications for their individual risk [4–7].

The Alzheimer's Prevention Initiative (API), established in 2010, is a collaborative research program led by Banner Alzheimer's Institute in partnership with other key organizations working to accelerate the evaluation of interventions to prevent AD dementia [4,8]. In 2012, API received a National Institutes of Health (NIH) grant to help support the Colombia Autosomal Dominant AD Trial (NCT01998841), the first funded prevention trial of an investigational disease-modifying treatment in cognitively unimpaired mutation carriers and noncarriers from the world's largest autosomal dominant AD kindred. Because many kindred members do not want to know their genetic status and there was no established paradigm for genetic disclosure in Colombia, this ongoing study includes both mutation carriers who are randomized to active treatment or placebo and noncarriers who receive placebo, and it does not include genetic disclosure [4].

In 2013, API received an NIH grant to help support Generation Study 1 (NCT02565511), the first of two complementary trials collectively referred to as the Generation Program and the first funded prevention trial of an investigational disease-modifying treatment in persons at genetic risk for late-onset AD [9,10]. Because this ongoing trial is studying cognitively unimpaired 60–75-year-old persons with two copies of the apolipoprotein E (*APOE4*) allele, the major genetic risk factor or AD, a mechanism was needed to provide *APOE4* homozygotes information about their genetic risk before their enrollment. Generation Study 2 (NCT03131453) was subsequently initiated in cognitively unimpaired *APOE4* carriers, including *APOE* ε4 heterozygotes with a positive amyloid positron emission tomography (PET) scan and additional *APOE4* homozygotes irrespective of their amyloid PET results [9,10]. Because it is one of the enrollment criteria, participants in Generation Study 2 must also receive information about their *APOE* test results, alone or in combination with their amyloid PET results. The design, rationale, and methodology of the API Generation Program has been published previously [10].

The joint practice guidelines for genetic counseling and testing for AD from the American College of Medical Genetics and Genomics as well as the National Society of Genetic Counselors recommend against *APOE* genetic susceptibility testing in clinical practice. The rationale for this recommendation is the limited clinical utility and prognostic value of testing in ordinary clinical use in individual patients and the potential for unintended psychological and social harms (e.g., distress, genetic discrimination) [11]. However, in a research context, *APOE* testing is a useful tool to identify potential participants for AD prevention studies and is the only context under which the National Institute on Aging recommends *APOE* testing [12]. In cases where *APOE* testing of cognitively unimpaired

individuals is necessary, the American College of Medical Genetics and Genomics as well as National Society of Genetic Counselors joint practice guidelines recommend counseling and disclosure be completed with a qualified genetics professional with a protocol modeled after the genetic testing protocol for Huntington's disease (HD) [13], which is based on the International Huntington Association and World Federation of Neurology Research Group on Huntington's Chorea Guidelines, as it is considered by many to be the gold standard for genetic testing for adult onset conditions [14]. The HD protocol incorporates multiple in-person visits that include one or two pretesting genetic counseling sessions incorporating mental health and neurological assessments, followed by genetic testing, a return visit for disclosure of results and counseling support, and finally a follow-up visit or a phone call [13,14].

Available data suggest that *APOE* disclosure using traditional genetic counseling and disclosure protocols, such as those modeled after the HD protocol guidelines, can be conducted safely and effectively [15–19]. Although traditional models of *APOE* genetic counseling and disclosure have been shown to be effective, they are not scalable. To identify the number of participants with the appropriate *APOE* results required by preclinical AD studies, a substantial number of persons will need to learn their *APOE* results. For example, to enroll approximately 3000 individuals into the Generation Program trials, we estimate that many more thousands of individuals will need to undergo genetic testing and learn their *APOE* results. Previous research studies developed condensed standardized *APOE* genetic counseling and disclosure protocols, providing written educational precounseling materials in lieu of the traditional in-person educational pretest counseling session to reduce trial site and participant burden. Compared with the traditional model, this condensed protocol was found to be equivalent in terms of participants' understanding and test-related distress and required significantly less face-to-face clinician time [20,21]. Although most studies using either traditional or condensed protocols report no significant increases in depression or anxiety symptoms among participants learning their *APOE* results, it is important to note that these outcomes have been studied in restricted settings and populations, with relatively few individuals at the highest risk level (i.e., *APOE4* homozygotes) or those close to the estimated age of symptom onset. These studies typically involved disclosure provided by expert genetic counselors to generally well-educated at-risk middle-aged individuals (based on family history of AD) who volunteered to learn such information and were screened to confirm psychological well-being before counseling and disclosure [15–18,21].

Recognizing the significance and sensitive nature of disclosing this type of information, as well as the need to address the scale of *APOE* genetic counseling and disclosure required by the Generation Program trials, the API team established a multidisciplinary Genetic Testing, Counseling, and Disclosure (GTCD) Committee to develop an *APOE* genetic counseling and disclosure process to responsibly provide participants with clear and consistent communication of genetic information in the Generation Program and to serve as a model for dissemination into clinical practice, complementing processes developed by other large-scale AD prevention programs for communication of biomarker results [22,23]. This article describes the rationale for, and methods used to develop the API Genetic Counseling and Disclosure Process, as well as challenges and future directions.

2. Methods

2.1. Process development

The API team recognized early in the planning stages for the Generation Program the need for special attention and consultation from qualified experts in the development of a program-specific *APOE* genetic counseling and disclosure process. The GTCD Committee was established to inform and guide the design of the API Genetic Counseling and Disclosure Process for use in the Generation Program. It comprises physicians, social science researchers, health educators, legal experts, and genetic counselors, with expertise in AD, medical ethics, and disclosure of genetic risk factors. At the start of protocol development, the GTCD Committee met every 2 weeks by telephone and approximately quarterly in person. The committee continues to meet monthly by telephone during study implementation. The committee operationalized eight components comprising the API Genetic Counseling and Disclosure Process whose core features include guidelines for *APOE* testing and reports and providers of disclosure, standardized education and structured content of counseling and disclosure sessions, in-clinic assessment of well-being, assessment of psychological readiness for disclosure and evaluation of *APOE* disclosure impact (Fig. 1).

2.2. APOE genetic testing

Some individuals enroll in the Generation Program already knowing their *APOE* genotype from prior genetic testing (e.g., via direct-to-consumer testing); nevertheless, for quality control and standardization purposes, the API Genetic Counseling and Disclosure Process requires all participants to complete an *APOE* counseling and disclosure session. This requirement also ensures all participants have access to the same information about *APOE* and the associated risk for AD, as well as providing all participants an opportunity to discuss their results with a provider. All participants complete *APOE* testing via the study's central laboratory as part of screening regardless of prior testing, but in cases where a report for previous *APOE* genotyping can be obtained and confirmed as completed by an appropriately certified laboratory (per local regulations, e.g., Clinical Laboratory Improvement Amendments and College of American Pathologists accreditation), these initial results may be used for the *APOE* counseling and disclosure session.

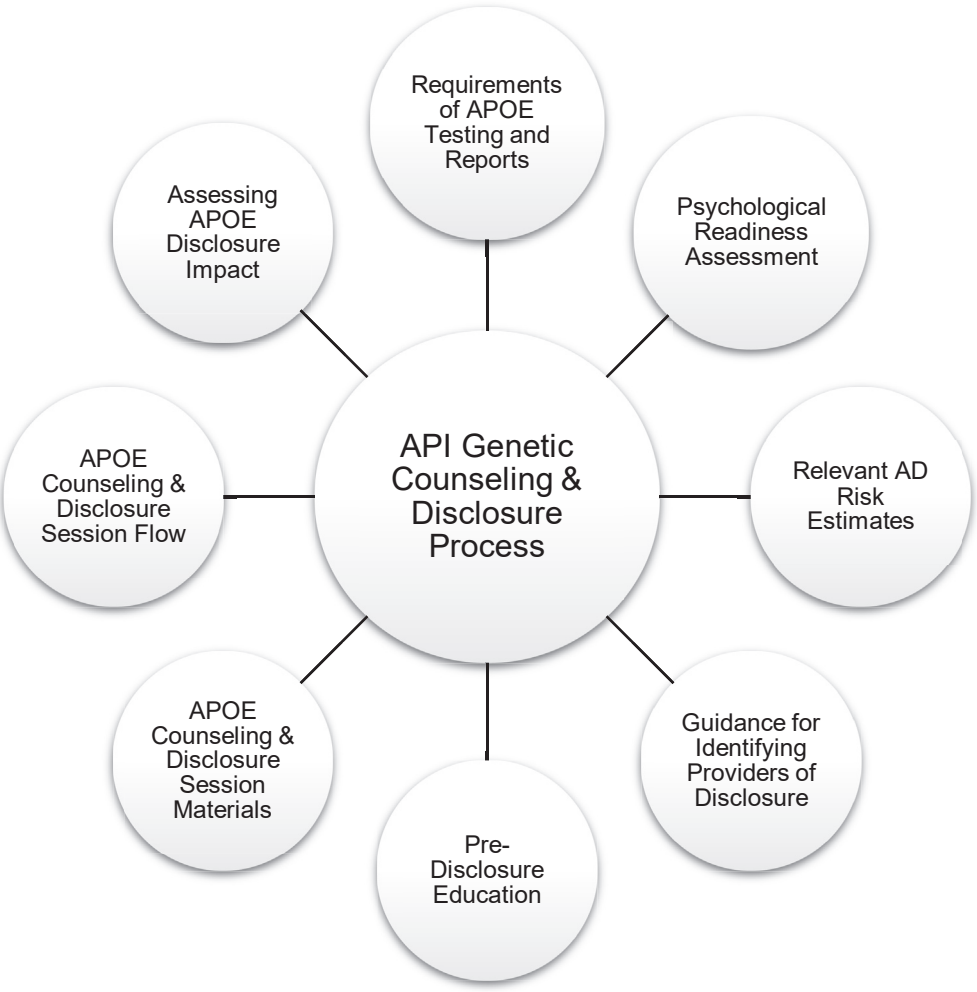

Fig. 1. Alzheimer's Prevention Initiative Genetic Counseling and Disclosure Process components. Abbreviations: *APOE*, apolipoprotein E; API, Alzheimer's Prevention Initiative; AD, Alzheimer's disease.

2.3. *Assessing psychological readiness for* APOE *disclosure*

To reduce the risk of negative psychological reactions to disclosure of *APOE* results, measures to assess psychological readiness to receive results are administered by trained site personnel before the genetic counseling and disclosure session can proceed. The 15-item version of the Geriatric Depression Scale (GDS) [24] and the Six-Item Subset of the State-Trait Anxiety Inventory for Adults (STAI-AD) [25,26] are used as assessments of psychological readiness in both Generation Program studies as they are well-known measures of mood and anxiety with established clinically meaningful defined score ranges. Generation Study 2 adds the electronic version of the Columbia Suicide Severity Rating Scale (C-SSRS) [27] to assess current and prior lifetime suicidal ideation and behaviors, whereas in Generation Study 1, this was assessed by clinical judgment before genetic disclosure. However, the C-SSRS is administered to *APOE4* homozygotes in part 2 of Generation Study 1 as described previously [10].

In Generation Study 1, psychological readiness assessment scores above a specified threshold (GDS >6 and STAI-AD >19) results in automatic exclusion, whereas scores within flagged ranges require additional investigator review for inclusion, with special attention to responses on specific questions (Table 1). Generation Study 2 also uses GDS and STAI-AD as assessments of psychological readiness, with specified scores requiring additional investigator review for inclusion (Table 1), but no exclusionary cutoffs are included for GDS or STAI-AD to allow for increased flexibility for investigators to use their clinical judgment when evaluating participants' psychological readiness. However, Generation Study 2 adds the electronic version of the C-SSRS as an additional measure of psychological readiness, resulting in exclusion of participants who report active suicidal ideation (with at least some intent to act) in the past 6 months and/or those reporting suicidal behavior (not including nonsuicidal self-injurious behavior) in the past 2 years. If participants are excluded from study participation based on suicidality, participant safety and

Table 1
Psychological readiness criteria

Generation Study 1
- Psychological readiness to receive *APOE* genotype information based on predisclosure rating scales, specifically:
  - GDS Short Form total score <6.
    If the score is between 6 and 10 (inclusive), the participant can only be included based on investigator's judgment assessing in particular the scores of the questions:
    i. Item 3: "Do you feel your life is empty?"
    ii. Item 6: "Are you afraid that something bad is going to happen to you?"
    iii. Item 12: "Do you feel pretty worthless the way you are now?"
    iv. Item 14: "Do you feel your situation is hopeless?"
  - Six-Item Subset Inventory of the STAI-AD total score <17.
    - If the score is between 17 and 19 (inclusive), the participant can only be included based on the investigator's judgment

Generation Study 2
- Lacking psychological readiness to receive *APOE* genotype/amyloid status results, as assessed based on investigator's judgment supported by the predisclosure rating scales:
  - GDS Short Form total score > 6
  - Six-Item Subset Inventory of the modified STAI-AD total score >17
- C-SSRS exclusion criteria
  - Reports active suicidal ideation with at least some intent to act, with or without a specific plan, if this ideation occurred in the past 6 months
  - Reports suicidal behavior (not including nonsuicidal self-injurious behavior) if this behavior occurred in the past 2 years before screening

Abbreviations: *APOE*, apolipoprotein E; GDS, Geriatric Depression Scale; STAI-AD, State-Trait Anxiety Inventory for Adults; C-SSRS, Columbia Suicide Severity Rating Scale.

well-being continue to be monitored per trial protocol. The process for referral and follow-up with mental health resources varies by country as does site access to mental health professionals (e.g., some site investigators are psychiatrists).

2.4. Risk estimates

To provide estimates of risk for development of mild cognitive impairment (MCI) or dementia due to AD tailored to the Generation Program study population, data from four large prospective longitudinal studies were analyzed for the incidence of MCI or dementia among initially cognitively unimpaired individuals aged 60–75 stratified by *APOE* genotype. The results from these analyses were published previously [28]. In brief, 5-year risk estimates by age group (e.g., 60–64, 65–69) were found to be highly variable in comparison to lifetime risk estimates (defined as through age 85); therefore, the API Genetic Counseling and Disclosure Process provides lifetime risk estimates in the corresponding *APOE* genetic counseling and disclosure materials [28]. In addition, the AD risk estimates developed for the Generation Program are lower than those published previously and used for *APOE* disclosure in the REVEAL studies and by direct-to-consumer genetic testing companies [29,30]. These lower risk estimates supported the decision to require all Generation Program participants to complete a genetic counseling and disclosure session, regardless of prior knowledge of *APOE* status, to ensure all participants are provided with these updated population-specific AD risk estimates.

2.5. Genetic counseling and disclosure providers

Multiple strategies are used to address limited site access to genetic counselors or other genetics-trained professionals. In the United States and Canada, sites can not only use local providers of genetic counseling and disclosure but also have access to centralized remote genetics services, where an offsite genetic counselor completes the *APOE* counseling and disclosure session via telephone or videoconference. Outside the United States and Canada, local providers are used primarily. Local providers of genetic counseling and disclosure must be qualified per local laws and regulations governing genetic counseling and associated licensure requirements of providers. In areas where no regulations exist, the Sponsors recommend that providers of genetic counseling and disclosure be trained clinical professionals with an advanced understanding of genetics and experience with providing potentially sensitive medical results. In cases of uncertainty, qualifications of the proposed provider are reviewed and approved by the Sponsors.

2.6. Predisclosure genetic education materials

To reduce participant burden and address the considerable number of *APOE* genetic counseling and disclosure sessions expected to meet enrollment goals of the Generation Program, the API Genetic Counseling and Disclosure Process uses a condensed model that can be completed in a single visit to a Generation Program study site. To accommodate a condensed model, we developed self-directed learning materials, including an Educational Predisclosure Video and Disclosure Informational Brochure (both accessible to participants before the genetic counseling and disclosure visit) covering content typically addressed in a pretesting genetic counseling session. The Video and Brochure provide a summary of the *APOE* gene and its relationship to AD, as well as considerations for learning one's *APOE* genotype for both the participant and their family (e.g., potential emotional responses, implications of AD risk for blood relatives). The Video incorporates several

multiple-choice questions with feedback explaining the correct response to help confirm and reinforce participant understanding. Participants are strongly encouraged to review these materials in advance of the *APOE* counseling and disclosure session to orient and familiarize themselves with the information addressed during the session. These key points are also included in the study of informed consent form to ensure participants are presented with this information before enrolling in the trial.

2.7. Genetic counseling and disclosure session materials

Several supportive materials are used in the API Genetic Counseling and Disclosure Process to help standardize the *APOE* counseling and disclosure session. A Genetic Counseling and Disclosure Session Handout and a set of Genetic Counseling and Disclosure Session Talking Points (Table 2) help standardize the content of the session. The provider uses the Handout as a visual aid during the counseling and disclosure session (participants are provided with a copy for note taking and to keep) and uses the Talking Points as a reference guide for the session. The Talking Points are intended to help address the variability of experience and expertise providers may have in educating participants in genetics and with disclosing *APOE* results. The Talking Points highlight key topics to be addressed during the session but are not intended to be exhaustive or restrictive.

Participants who enroll in the Generation Program already knowing their *APOE* results are required to complete an *APOE* counseling and disclosure session as part of the API Genetic Counseling and Disclosure Process, but a slightly modified set of talking points are used with these participants (See Supplementary Table 1). Talking points for participants already aware of their *APOE* genotype do not include review of disclosure implications or confirmation of their desire to learn results (as they are already known) but add a discussion of the previous disclosure experience and any impact it had on the participant and their family.

APOE Risk Estimate Summary Sheets are available for each possible genotype and provided to participants after the session to serve as a record of their results and the associated risk information reviewed during the session. For purposes of the Generation Program, a Genetic Counseling and Disclosure Session Manual outlines the entire API Genetic

Table 2
Genetic counseling and disclosure session talking points for participants undergoing first time disclosure of their *APOE* results

API Genetic Counseling and Disclosure Process: genetic counseling and disclosure session talking points with individuals receiving first-time* disclosure

1. Introduction to session
2. Review purpose of session and confirm the individual's interest in participation
3. Review family history, with focus on AD/dementia
4. Basic clinical description of AD, MCI, and dementia
5. Impact of *APOE* on AD risk
   a. Cannot definitively predict or rule out development of AD
   b. No medical management currently available based on *APOE* status
   c. Review three possible results and associated AD/MCI risk
      i. Zero copies (ε3/ε3, ε2/3, ε2/ε2)
      ii. One copy (ε3/ε4, ε2/ε4)
      iii. Two copies (ε4/ε4)
6. Inheritance of *APOE* gene; address possible implications for children and siblings
7. Considerations for learning *APOE* results
   a. Psychological impact
   b. Familial impact
   c. Clinical research impact
8. Review Genetic Information Nondiscrimination Act (pertains to United States only)
9. Address specific concerns or considerations about learning *APOE* result
10. State option to either proceed with disclosure of *APOE* genetic testing results, postpone disclosure to later date, or decline disclosure of *APOE* results
    a. If proceeding with disclosure, talking points 11–16 would follow
    b. If postponing, review plan for participant to recontact site when ready to proceed with disclosure. Address remaining questions and concerns before ending the session
    c. If declining disclosure, participant would be given time to address their questions or concerns before ending the session
11. Disclosure of *APOE* result
    a. If participant receives genotype containing rare ε3 (ε3r) variant, provide education and risk assessment for corresponding ε3 genotype and address information in the "Rare *APOE* ε3r gene variant" slide in the standardized *APOE* risk handout
12. Disclosure of AD risk information
    a. Provide comparison for other *APOE* genotypes to provide context
13. Allow participant to ask questions and/or discuss issues of concern or interest that are of most importance to them after learning result
14. Address participant's emotional response to result (if any)
15. Review plan for follow-up phone calls by study coordinator
16. State eligibility for next steps in research participation

Abbreviations: *APOE*, apolipoprotein E; API, Alzheimer's Prevention Initiative; AD, Alzheimer's disease; MCI, mild cognitive impairment.
*Talking points for participants already aware of their *APOE* status is available in the supplemental online information.

Counseling and Disclosure Process. The materials used in the Process were written in American English but were designed to be generally applicable worldwide, often only requiring translation and/or subtitles. The materials were designed to be edited easily (e.g., made with commonly available software packages in editable formats) in case modifications are needed for cultural adaptation. The API Genetic Counseling and Disclosure Process materials are available on request at the discretion of the authors.

2.8. Genetic counseling and disclosure sessions

The *APOE* counseling and disclosure session begins with a brief review of the educational content from the Educational Predisclosure Video and Disclosure Informational Brochure, as well as a discussion of the participant's family history, feelings toward *APOE* disclosure, and considerations for learning one's *APOE* results. Before disclosure of *APOE* results and associated risk estimates, the provider is required to confirm the participants' continued desire to learn their *APOE* results (for people who do not already know their *APOE* genotype). After disclosure, with consideration given to the emotional and informational needs of the participant, the provider also discusses inheritance implications, degree of risk comparisons, potential risk modifiers, and offers resources for more information. The Risk Estimate Summary Sheet corresponding with the participant's *APOE* result is given to the participant at the end of the session. All genetic counseling and disclosure sessions are completed with the participant at a study site, even if the site is using remote genetic services, to ensure study staff are immediately available if needed. Post-disclosure follow-up with the participant can be completed by telephone or in person. The materials used in the API Genetic Counseling and Disclosure Process were designed to be easily adaptable to local standards and regulations. Fig. 2 presents a flowchart summarizing the API Genetic Counseling and Disclosure Process.

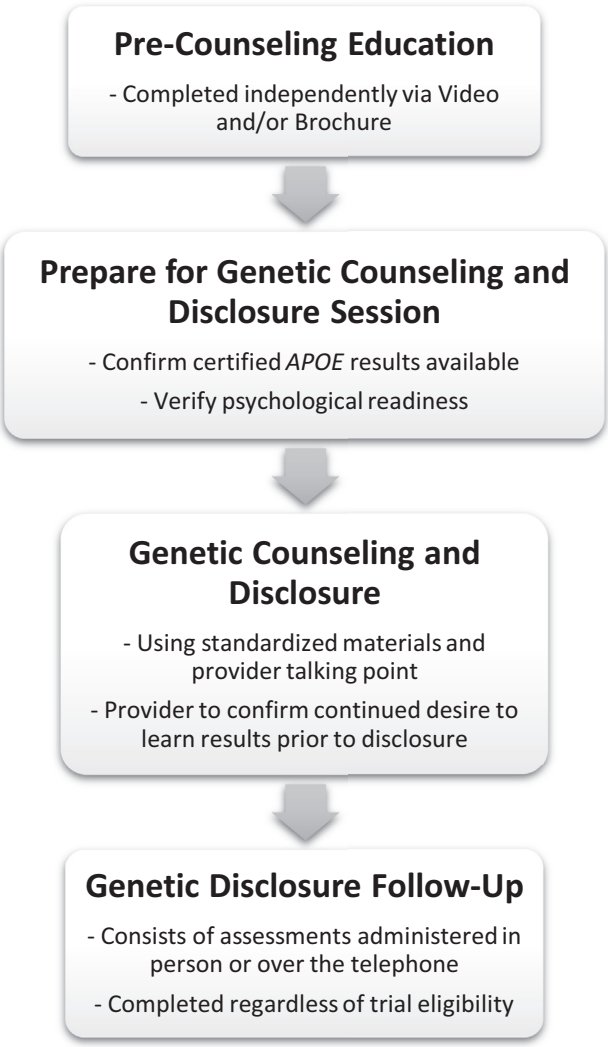

Fig. 2. Alzheimer's Prevention Initiative Genetic Counseling and Disclosure Process flow. Abbreviation: *APOE*, apolipoprotein E.

2.9. Assessing impact of APOE disclosure

Given the limited available data on the outcomes of *APOE* disclosure, specifically in the context of clinical trials, and the desire to demonstrate the utility of the process, the API Genetic Counseling and Disclosure Process incorporates follow-up measures to assess the impact of participants learning their *APOE* results. Generation Study 1 includes a robust battery assessing impact of *APOE* disclosure administered 2–7 days, 6 weeks, 6 months, and 12 months after disclosure (Table 3). Assessments included in Generation Study 1 genetic disclosure follow-up period include measures of participant psychological well-being, understanding and retention of information presented throughout the API Genetic Counseling and Disclosure Process, perceptions of perceived risk and threat of AD, and assessments of the general impact of *APOE* testing and motivation for learning these results, as well as participant satisfaction with the genetic services provided, including satisfaction with remote counseling, when applicable.

In contrast, Generation Study 2, which began recruitment approximately 18 months after Generation Study 1, includes an abbreviated battery, with only a 2–7-day follow-up using the GDS and STAI-AD, because thorough *APOE* disclosure follow-up is being completed in an adequately large sample as part of Generation Study 1. To reduce participant burden, all postdisclosure follow-up assessments may be administered over the phone or in person for both studies. The schedule of assessments for genetic disclosure follow-up in both Generation Study 1 and Generation Study 2 is provided in Table 3. It is important to note that key safety assessments (e.g., assessment of adverse events and serious adverse events, assessments of suicidality) are completed in all participants throughout both studies, independent of *APOE* disclosure follow-up.

Table 3
Generation Program genetic disclosure follow-up schedule of assessments

Visit timepoint	Day 1 (disclosure visit)	2–7 Days	6 Weeks	6 Months	12 Months
Visit number	1	101	102	103	104
Generation Sudy 1					
Genetic counseling	X				
Disclosure of genotype	X				
Six-Item Subset of the STAI-AD [25,26]	X	X	X	X	X
GDS [24]	X	X	X	X	X
Knowledge of genetic disease [31–33]	X	X	X	X	X
Disease-specific distress (adapted Impact of Events Scale) [34–36]	X	X	X	X	X
Perceived risk of AD [37,38]	X	X	X	X	X
Perceived threat about AD [39]	X	X	X	X	X
Motivation for learning *APOE* results	X				
REVEAL IGT-AD [40]		X	X	X	X
Satisfaction with remote counseling [41–43]		X			
Satisfaction with genetic services [44]		X			
Generation Study 2					
Genetic counseling	X				
Disclosure of genotype	X				
Six-Item Subset of the STAI-AD [25,26]	X	X			
GDS [24]	X	X			

Abbreviations: STAI-AD, State-Trait Anxiety Inventory for Adults; GDS, Geriatric Depression Scale; AD, Alzheimer's disease; *APOE*, apolipoprotein E; IGT-AD, Impact of Genetic Testing for Alzheimer's disease.

3. Discussion

At this time, *APOE* counseling and disclosure are usually not recommended in the clinical setting because of lack of clinical utility [11]; however, when disclosure is necessary, the recommended traditional models of genetic counseling and disclosure require multiple visits and a substantial amount of time with a genetics-trained professional [13,14]. The Generation Program (and potentially other future preclinical AD trials) requires identification of individuals at high risk for developing dementia due to AD based in part on *APOE* genotype [3,9,10]. Thousands of individuals will need to undergo *APOE* genetic testing, counseling, and disclosure as part of the sizable recruitment and screening funnel required to meet prevention study program enrollment goals [45]. As such, an alternative to traditional models of genetic counseling and disclosure is needed to provide comprehensive standardized counseling and disclosure of *APOE* results efficiently, safely, and effectively in the context of AD prevention trials. The API Genetic Counseling and Disclosure Process was designed to meet these needs for the Generation Program and to serve as a much-needed framework for future endeavors requiring large-scale *APOE* genetic counseling and disclosure with cognitively healthy older adults.

Enlisting multidisciplinary experts was critical in the design of the API Genetic Counseling and Disclosure Process. Including committee members with wide-ranging areas of expertise and backgrounds led to the creation of an ethically sound, practicable, and comprehensive process strengthened by the wealth of knowledge and insight offered by the GTCD committee. Numerous factors were taken into consideration, including how best to provide comprehensive standardized genetic counseling and disclosure-related information to participants. In the Generation Program, *APOE* counseling and disclosure is completed at sites across the world by providers with varying levels of relevant training and experience. To ensure consistency of communication of information to participants before and during the *APOE* counseling and disclosure session, the GTCD committee developed educational and session materials (e.g., Education Predisclosure Video, Genetic Counseling and Disclosure Session Handout, Genetic Counseling and Disclosure Session Talking Points) to direct the API Genetic Counseling and Disclosure Process and support providers of genetic counseling and disclosure, especially those with limited experience in delivering *APOE* results. To provide applicable estimates of *APOE*-associated risk of developing MCI or dementia because of AD for use in the API Genetic Counseling and Disclosure Process materials, updated lifetime risk estimates tailored to the Generation Program study population were calculated based on four large longitudinal studies [28].

It was also necessary to address the logistical considerations of completing a substantial number of *APOE* counseling and disclosure sessions. To reduce participant burden and amount of time needed with a provider, the API Genetic Counseling and Disclosure Process is completed during one visit to the study site. To facilitate a condensed model, participants complete precounseling education independently and/or remotely via a web-accessible Education Predisclosure Video and written Disclosure Informational Brochure instead of the pretest in-person genetic counseling visit typically included in traditional models of genetic counseling and disclosure [14]. Also, all

postdisclosure participant follow-up may be completed over the phone, further reducing the number of visits to the study site.

Preclinical AD studies such as the Generation Program are conducted globally at numerous sites with varying levels of access to genetics-trained professionals with varying experience disclosing *APOE* results. The API Genetic Counseling and Disclosure Process was designed to provide a consistent participant experience regardless of the genetic counseling and disclosure provider's experience level by incorporating standardized materials, including a Genetic Counseling and Disclosure Session Handout and Genetic Counseling and Disclosure Session Talking Points to guide the session. In addition, *APOE* Risk Estimate Summary Sheets are available for each possible genotype result and are provided to participants after the session to serve as a record of their results and the associated risk information reviewed during the session.

Another way to improve access to professionals trained in genetics is the use of remote genetics services. Several studies in cancer have shown telephone-based delivery of genetic results to be safe [46–51], and one study has shown delivery of *APOE* results by telephone to be equivalent to in-person sessions on scores of anxiety, depression, and test-related distress [18]. Currently, only Generation Program trial sites in the United States and Canada have access to centralized remote genetics services; however, the comparison of telephone-versus videoconferencing-based remote disclosure is being assessed at some sites in the United States as an investigator-initiated ancillary study (NCT02978729) to better understand implications of remote delivery modality [52]. Data from this ancillary study are being collected and will be shared in a future article.

The API Genetic Counseling and Disclosure Process was also designed to protect and monitor participant safety and well-being. As in previous research investigating impact of *APOE* disclosure, measures verifying psychological well-being are administered before the genetic counseling and disclosure session can proceed. Several assessments intended to evaluate psychological readiness to receive *APOE* results are administered, and in conjunction with investigator judgment, are used to determine whether it is appropriate for the participant to continue with *APOE* counseling and disclosure. Given the limitations of available research assessing the impact of *APOE* disclosure, particularly in the context of clinical trials, the API Genetic Counseling and Disclosure Process includes measures assessing psychological well-being as well as assessments evaluating how learning this information affects participants' understanding of, feelings toward, and beliefs about AD. These outcomes of *APOE* disclosure are being evaluated across all sites to inform real-world variation outcomes in a global trial. These data are being collected, and we look forward to reporting the results in the future.

The work done to develop the API Genetic Counseling and Disclosure Process for return of *APOE* results to cognitively normal AD prevention study participants complements processes developed by the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Study to disclose amyloid imaging results in the context of a preclinical AD trial [22] as well efforts from the European Prevention Alzheimer's Disease project assessing perspectives related to communication of biomarker-based risk of AD [23]. These programs, along with our work, will likely inform future strategies for communicating biomarker-based AD risk results to optimize outcomes in both the research and clinical settings.

Although the API Genetic Counseling and Disclosure Process offers a framework to complete large-scale *APOE* genetic counseling and disclosure in the context of an AD prevention clinical trial, we acknowledge several limitations. First, the API Genetic Counseling and Disclosure Process has only been implemented in two companion AD prevention studies of similar design but was designed to serve as a framework informed by standard genetic counseling and education principles to provide standardized *APOE* counseling and disclosure that accounts for anticipated real-world practice variations. For example, the API Genetic Counseling and Disclosure Process has already served as the foundation for the amyloid disclosure process in Generation Study 2. Second, applicability of the API Genetic Counseling and Disclosure Process outside a clinical trial setting is unclear as it has only been implemented as part of the Generation Program and has yet to be tested in a nonresearch-based clinical setting and population. In addition, to implement the API Genetic Counseling and Disclosure Process for another purpose, several of the materials may need to be updated and modified as those used in the API Genetic Counseling and Disclosure Process are tailored to the Generation Program. Certain materials may also need to be updated as the field's understanding of *APOE* and its associated risk of AD evolves over time. Third, measures of *APOE* disclosure impact included in the Generation Program focus on participant safety, well-being, understanding of and thoughts about AD, but other areas of impact warrant investigation. As such, additional areas of impact are being assessed as ancillary studies, including whether disclosure of *APOE* results is associated with worsening of subjective and objective cognitive functioning and stigma, as well as assessing potential differences based on delivery modality of remote genetic services (i.e., telephone vs. videoconference) [52].

3.1. Future directions

The API Genetic Counseling and Disclosure Process provides a novel framework for completing *APOE* counseling and disclosure in the context of AD prevention trials, such as those in our API studies. The *APOE* disclosure impact data we are collecting will help us understand the risks and benefits of modifying traditional

genetic counseling and disclosure models and set the stage for future adaptations of the current disclosure model in the research and clinical settings. Although comprehensive disclosure outcome data are being collected as part of the Generation Program and several ancillary studies are underway, additional areas of *APOE* disclosure impact warrant further examination, including evaluation of potential modifications to health and lifestyle behaviors, changes in financial behaviors, employment, and other economic factors, as well as potential impact of stigma and discrimination in response to *APOE* disclosure. It is imperative that we better understand the impact of *APOE* disclosure as an increasing number of individuals are learning this information as part of research and other activities, notably direct to consumer genetic testing [53].

Incorporating additional risk factors and modifiers to create a more comprehensive and individualized assessment of AD risk is another area warranting further study. For example, because PET, cerebrospinal fluid, and promising blood-based biomarker measurements may be used to screen or select participants in AD prevention studies, it will help to further optimize our approach to estimate a person's AD risk based on a combination of biomarker and *APOE* genotype results [3,54]. It will also be beneficial to understand better the impact of other potential modifiers (e.g., sex, health conditions) on personalized risk estimates for developing MCI or dementia because of AD. In addition, future research may not just rely on the *APOE* gene to identify participants at risk for AD but may use polygenic risk scores [55]. Better understanding the various risk factors, how they interact, and implications of various modifiers could eventually lead to the creation of a personalized AD risk calculator similar to the one developed by the American College of Cardiology and American Heart Association, which provides a personalized numerical risk value of developing atherosclerotic cardiovascular disease based on variety factors [56].

4. Conclusion

As the number of AD prevention studies continues to increase, an alternative to traditional genetic counseling and disclosure models is needed because of the substantial number of visits and face-to-face clinician time required, which is not always feasible in the context of a clinical trial. To address this need, the API Genetic Counseling and Disclosure Process was developed to provide a comprehensive and standardized alternative process for *APOE* counseling and disclosure in the Generation Program and to serve as a framework for large-scale *APOE* genetic counseling and disclosure programs in the future. The *APOE* disclosure impact data being collected will be vital in helping to better understand the risks and benefits of modifying traditional genetic counseling and disclosure models and will likely inform future adaptations to optimize patient outcomes for both the research and clinical settings.

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Authors' contributions: All authors participated in the study design, implementation, and/or conduct of the API Genetic Counseling and Disclosure Process. All authors contributed to the review of the protocol and approved the final article.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.trci.2019.09.013.

RESEARCH IN CONTEXT

1. Systematic review: We used sources such as PubMed to review the literature on genetic counseling and disclosure, with a focus on disclosure of apolipoprotein E (*APOE*) for risk of Alzheimer's disease.
2. Interpretation: The Alzheimer's Prevention Initiative's Genetic Counseling and Disclosure Process consists of eight components whose core features include guidelines for *APOE* testing requirements and providers of disclosure, standardized education and structured content of disclosure sessions, assessment of well-being and psychological readiness for disclosure, and evaluation of disclosure impact. The process provides a framework for large-scale disclosure of *APOE* genotype results to study participants and serves as a model for disclosure of biomarker results.
3. Future directions: Results from these studies will help us understand the impact of *APOE* disclosure as well as the implications of modifying traditional counseling and disclosure models and set the stage for future adaptations of the current model in research and clinical settings.

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