PI: **Bloss, Cinnamon S**	Title: Response to Testing Among Individual Consumers of DTC Personal Genomics Services	
Received: 06/17/2009	FOA: PA09-164	Council: 01/2010
Competition ID: ADOBE-FORMS-A	FOA Title: NIH EXPLORATORY/DEVELOPMENTAL RESEARCH GRANT PROGRAM (PARENT R21)	
1 **R21 HG005747-01**	Dual:	Accession Number: 3206388
IPF: 2054901	Organization: SCRIPPS HEALTH	
Former Number:	Department: Scripps Genomic Medicine	
IRG/SRG: ELS	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 75,000 Year 2: 75,000	Animals: N Humans: Y Clinical Trial: N Current HS Code: 30 HESC: N	New Investigator: N Early Stage Investigator: N
Senior/Key Personnel:	*Organization:*	*Role Category:*
Cinnamon Bloss PhD	Scripps Health	PD/PI
Eric Topol MD	Scripps Health	Faculty
Sarah Murray Ph.D.	Scripps Health	Faculty
Nicholas Schork Ph.D.	Scripps Health	Consultant
Lisa Madlensky PhD	University of California, San Diego	Consultant

Appendices

Appendix - irb approval letter,Appendix - irb-approved sghi 3-month assessmen

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Appendix

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PROJECT ABSTRACT

Results from several genome-wide association (GWA) studies have recently emerged showcasing the discovery of specific genetic variations found to be associated with several common, complex diseases. Leveraging these findings and fueled by the rapidly decreasing costs of performing genome-wide single nucleotide polymorphism (SNP) scans, a small number of companies have begun offering tests that aim to calculate an individual's risk for these common diseases using this genome-wide technology, direct-to-consumer (DTC) over the internet. While the offering of these tests – both at this stage of scientific discovery and directly to the consumer – has been the subject of much intense controversy, it is nevertheless the case that many individual consumers are purchasing these products. Despite this, however, relatively little is known about the characteristics of consumers of DTC personal genomics services, including why they chose to pursue this type of testing, and perhaps most critically, how they are responding to their results. The Scripps Genomic Health Initiative (SGHI) represents an opportunity to begin to address these questions. The SGHI is a large longitudinal cohort study in which participants purchase the Navigenics Health Compass DTC genomic risk assessment product at a discounted rate and are administered baseline (i.e., pre-risk disclosure), as well as 3- and 12-month follow-up (i.e., post-risk disclosure) web-based demographic, family medical history, and behavioral health assessments. In addition, items pertaining to attitudes about genetic testing and the perceived impact of the results, including distress related to receiving information pertaining to one's genomic risk profile, are administered. The SGHI is, to a large degree, exploratory in that it is one of the first studies to evaluate response to testing among individual consumers of DTC personal genomics services. To date, over 4,000 individuals have enrolled in the SGHI, and although the ongoing recruitment of individuals into the study is currently funded, analysis of the assessment data that is being collected is unfunded. Therefore, we are requesting two years of funding via the NIH Exploratory/Developmental Research Grant Program (R21) for analysis of these data. Our specific aims are as follows: First we will characterize consumers of DTC personal genomics services in terms of their demographics, baseline level of genetic risk for disease, behavioral health characteristics, and attitudes regarding genetic testing. Second, we will assess response to testing among consumers with respect to general anxiety and distress related to testing, perception of new disease risk, changes in health behaviors, and attitudes regarding the impact of results. Third, we will evaluate potential moderators of response to testing, including demographic characteristics, perception of risk, risk estimates reported in the Health Compass, and utilization of genetic counseling services.

PROJECT NARRATIVE

The proposed project would leverage data from the Scripps Genomic Health Initiative (SGHI), a large longitudinal cohort study of over 4,000 consumers of GWAS-based DTC personal genomics services (i.e., specifically the Navigenics Health Compass product). We aim to characterize consumers of DTC personal genomics services, as well as assess behavioral and psychological response to DTC genetic testing, including potential moderators of response such as level of genetic risk and utilization of genetic counseling services. At this time there is essentially nothing known about the impact of this technology on consumers despite its relatively wide availability and the fact that many individual consumers have already purchased these products. Thus, the proposed work will provide an initial examination of these important questions to which timely answers are critical given efforts currently underway to determine how best to regulate the sale and use of these tests.

Scripps Genomic Medicine FACILITIES & OTHER RESOURCES

FACILITIES: Specify the facilities to be used for the conduct of the proposed research. Indicate the performance sites and describe capacities, pertinent capabilities, relative proximity, and extent of availability to the project. If research involving Select Agent(s) will occur at any performance site(s), the biocontainment resources available at each site should be described. Under "Other," identify support services such as machine shop, electronics shop, and specify the extent to which they will be available to the project. Use continuation pages if necessary.

Laboratory:

The Scripps Genomic Medicine Laboratory (SGM) has approximately 4,000 square feet of modern state-of-the-field dry lab space and is equipped for analysis of both high-dimensional SNP and resequencing data. In addition, SGM has approximately 2500 square feet of modern state-of-the-field molecular biology and genetics wet lab space with 6 laboratory bays that can accommodate 10-20 laboratory technicians. The wet lab is fully equipped for sample collection, DNA isolation, high-throughput genotyping, and sequencing.

Clinical:

N/A

Biocontainment Resources Available: Complete if research involving Select Agent(s) will occur at any performance site(s), otherwise indicate N/A.

N/A

Animal:

N/A

Computer:

Each member of the informatics and analysis component of Scripps Genomic Medicine, including Dr. Bloss, uses a laptop and/or state-of-the-field desktop computer. The laboratory has five UNIX machines, seven printers, wireless capabilities and current state-of-the-field commercial, computational, bioinformatic and statistical analysis software and libraries, including SPPS, SAS, MATLAB, Ingeunity, MetaCore, and the NAG libraries. As part of *The Scripps Research Institute's Supercomputing core* (http://www.scripps.edu/rc/), Dr. Bloss has access to two large SGI LINUX machines, a 32-bit LINUX cluster, and a 64-bit LINUX cluster. The SGI LINUX machine is a 128 CPU 1.3 Ghz Itanium-2 SGI 3700 server, with 128 GBytes of memory and one Terabyte of local disk space. The garibaldi LINUX cluster contains 800 2.33 GHZ Intel dual core XEON-EMT processors for a total of 1600 cpu's available for computations. The garibaldi cluster uses additional Intel dual core XEON-EMT processors for system functions. The bluefish LINUX cluster contains 1196 3.4 GHZ Intel XEON-EMT processors used for computations and additional Intel XEON-EMT processors are used for system functions. Between local and shared disks each cluster has over fifty Terabytes of disk space available for computational data. Both systems schedule jobs using the PBS batch queuing system to ensure maximum system throughput and fair access. In addition, as part of a collaboration between Scripps Genomic Medicine and the San Diego Supercomputer Center (SDSC; http://www.sdsc.edu/), Dr. Bloss has access to extremely large-scale high performance computers, including DataStar BM p-Series, which has 2528 Power4+ CPUs capable of 15.6 teraflops with 180 terabytes of storage; the TeraGrid IBM Cluster with 532 Itanium2 CPUs capable of 4.4 teraflops and 68 terabytes of storage; and an Intimidata Blue Gene eServer cluster with 6144 PowerPC CPUs capable of 17.2 teraflops and 25 terabytes of storage. The SDSC is also the world-leader in data archiving and cyberinfrastructure development.

Office:

Scripps Genomic Medicine is part of the *Scripps Translational Science Institute* (STSI) (http://STSIweb.org), which consists of 15,000 square feet of research offices dedicated to translational research in medicine. The informatics and analysis component of the STSI has offices to house eleven graduate/undergraduate students, four research faculty, three post-doctoral fellows, two research computing programmers, two visiting scholars, and one climate control computational server center.

Other:

The Scripps Research Institute has a number of molecular and computational biology core facilities available to Dr. Bloss (http://www.scripps.edu).

EQUIPMENT RESOURCES

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location and pertinent capabilities of each.

SCRIPPS GENOMIC MEDICINE

Statistical analysis software and libraries: SPPS, SAS, MATLAB, Ingeunity, MetaCore, and the NAG libraries
32-bit LINUX cluster
64-bit LINUX cluster
1 Analysis Server (HP DL585 2x3.0 GHz CPU, 32 GB RAM) with 18 TB storage
1 Oracle Server (HP DL585 2x3.0 GHz CPU, 32 GB RAM)) with 2 TB storage
1 Web server (HP DL360 2x3.0 GHz CPU, 4 GB RAM) with 125GB
1 Analysis Workstation/Server (HP DL385 2x3.0 GHz, 8 GB RAM) with 1 TB storage
1 File Server (Dell Server PE2900 2 X2.0 GHz Quad Core CPU, 4 GB RAM) with 3.5 TB storage

PHS 398 Modular Budget, Periods 1 and 2

OMB Number: 0925-0001

Budget Period: 1

Reset Entries | Start Date: 04/01/2010 | End Date: 03/31/2011

A. Direct Costs

	* Funds Requested ($)
* Direct Cost less Consortium F&A	75,000.00
Consortium F&A	25,000.00
* Total Direct Costs	100,000.00

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.	Salaries and Wage	14.7	54,921.00	8,073.00
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number): See Attached Letter with Budget Justification.

Indirect Cost Rate Agreement Date:

Total Indirect Costs: 8,073.00

C. Total Direct and Indirect Costs (A + B)

Funds Requested ($): 108,073.00

Budget Period: 2

Reset Entries | Start Date: 04/01/2011 | End Date: 03/31/2012

A. Direct Costs

	* Funds Requested ($)
* Direct Cost less Consortium F&A	75,000.00
Consortium F&A	25,000.00
* Total Direct Costs	100,000.00

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.	Salary and Wage	14.7	54,921.00	8,073.00
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number): See attached letter with the Budget Justification

Indirect Cost Rate Agreement Date:

Total Indirect Costs: 8,073.00

C. Total Direct and Indirect Costs (A + B)

Funds Requested ($): 108,073.00

PHS 398 Modular Budget, Periods 3 and 4

Budget Period: 3

Reset Entries | Start Date: | End Date:

A. Direct Costs

	* Funds Requested ($)
* Direct Cost less Consortium F&A	
Consortium F&A	
* Total Direct Costs	

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.				
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number)

Indirect Cost Rate Agreement Date | Total Indirect Costs

C. Total Direct and Indirect Costs (A + B) | Funds Requested ($)

Budget Period: 4

Reset Entries | Start Date: | End Date:

A. Direct Costs

	* Funds Requested ($)
* Direct Cost less Consortium F&A	
Consortium F&A	
* Total Direct Costs	

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.				
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number)

Indirect Cost Rate Agreement Date | Total Indirect Costs

C. Total Direct and Indirect Costs (A + B) | Funds Requested ($)

Tracking Number:GRANT10354920 Funding Opportunity Number:PA-09-164 Received Date:2009-06-17T13:38:58-04:00

PHS 398 Modular Budget, Periods 5 and Cumulative

Budget Period: 5

Reset Entries | Start Date: | End Date:

A. Direct Costs

	* Funds Requested ($)
* Direct Cost less Consortium F&A	
Consortium F&A	
* Total Direct Costs	

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.				
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number)

Indirect Cost Rate Agreement Date | Total Indirect Costs

C. Total Direct and Indirect Costs (A + B) Funds Requested ($)

Cumulative Budget Information

1. Total Costs, Entire Project Period

*Section A, Total Direct Cost less Consortium F&A for Entire Project Period	$	150,000.00
Section A, Total Consortium F&A for Entire Project Period	$	50,000.00
*Section A, Total Direct Costs for Entire Project Period	$	200,000.00
*Section B, Total Indirect Costs for Entire Project Period	$	16,146.00
*Section C, Total Direct and Indirect Costs (A+B) for Entire Project Period	$	216,146.00

2. Budget Justifications

Personnel Justification	1245-Budget Justification - Mo		Delete Attachment	View Attachment
Consortium Justification	1246-Budget Justification - C		Delete Attachment	View Attachment
Additional Narrative Justification		Add Attachment		

BUDGET JUSTIFICATION

Senior/Key Personnel

Cinnamon S. Bloss, Ph.D., Principal Investigator, Research Scientist, Scripps Genomic Medicine (Effort EFFORT months). Dr. Bloss is a clinical psychologist who has completed fellowships in statistical genetics and genomic medicine; she is now a junior investigator within the Scripps Translational Science Institute. Dr. Bloss has considerable specialty training in psychological assessment, specifically the assessment of neurocognitive functions in children and adults. During her fellowships, which were under the mentorship of Dr. Nicholas Schork, Dr. Bloss gained experience conducting analyses of large-scale candidate gene and whole-genome data, and is currently a lead scientist for the NHGRI/NIMH Genetic Association Information Network (GAIN)-funded Bipolar Genome-Wide Association (GWA) study. Dr. Bloss will devote 25% effort to this research and will oversee all of the work, including framing research questions, conducting statistical analyses of behavioral data, interpretation of findings, and preparation of manuscripts.

Eric J. Topol, M.D., Co-Investigator, Director, Scripps Translational Science Institute (Effort = EFFORT calendar months). Dr. Topol is Director of Scripps Genomic Medicine and the Scripps Translational Science Institute (STSI), Chief Academic Officer of Scripps Health, and Professor of Translational Genomics in the Department of Molecular and Experimental Medicine at The Scripps Research Institute. Dr. Topol is one of the most pre-eminent translational researchers in the world, having organized the renowned clinical research programs at the Cleveland Clinic, as well as orchestrating large-scale human genetics initiatives such as the GeneQuest cardiovascular genomics study. Dr. Topol has authored or co-authored more than 1,000 biomedical research articles that span all areas of translationally-oriented biomedical research. Dr. Topol is the principal investigator for the Scripps Genomic Health Initiative, and as such, will be responsible for managing the collaboration between the STSI, Navigenics, and Affymetrix. Dr. Topol will further serve as a genomic medicine expert, cardiovascular disease risk expert, and will assist with interpretation of findings from behavioral data analysis.

Sarah S. Murray, Ph.D., Co-Investigator, Director of Genetics, Scripps Genomic Medicine (Effort EFFORT calendar months). Dr. Murray is Director of Genetics at Scripps Genomic Medicine and Associate Professor of Translational Genomics in the Department of Molecular and Experimental Medicine at The Scripps Research Institute. Dr. Murray has a long history in both theoretical and applied genetics research. She has published over 50 articles in the human genetics literature that focus on both disease gene mapping and the discovery and analysis of DNA sequence polymorphism. Dr. Murray has been involved in the design of very large-scale genetics and genomics technologies that interrogate DNA sequence variation. For example, Dr. Murray was responsible for the design and choice of the content for the widely used Illumina whole-genome SNP genotyping chip products. Dr. Murray will leverage her expertise with respect to whole-genome arrays for SNP genotyping, as well as her background in genetic counseling, to assist with behavioral data analysis and interpretation of findings.

Nicholas J. Schork, Ph.D., Co-Investigator, Director of Biostatistics and Bioinformatics, Scripps Translational Science Institute (Gratis Effort). Dr. Schork is Director of Biostatistics and Bioinformatics for the Scripps Translational Science Institute and Director of Research at Scripps Genomic Medicine. Dr. Schork has expertise in longitudinal data analysis, statistical genetics, bioinformatics, and biostatistics. He has published over 230 articles in the area of genetic dissection of complex phenotypes, which includes both methodological and applied work. Dr. Schork's salary is covered by his appointment as Director of Biostatistics and Bioinformatics for the Clinical and Translational Science Award (CTSA)-funded Scripps Translational Science Institute (STSI), whose NIH mandate is to further translational genomics and foster interdisciplinary human genomic studies. Dr. Schork will assist with and oversee aspects of the data analysis for the proposed work, including analyses requiring sophisticated longitudinal methods and methods that address issues related to attrition.

Other Personnel

To Be Named, **Computer Programmer** (Effort = 1.20 calendar months). A computer programmer will be assigned to the project at the appropriate time point to assist with database management, import and export of data into relevant statistical analysis programs, and data queries.

General Accounting
4275 Campus Point Court, CP111
San Diego, CA 92121
Direct (858) 678-7275 FAX (858) 678-6164

Scripps

March 26, 2009

National Institute for Health
9000 Rockville Pike
Bethesda, MD 20892

Re: Scripps Health Indirect Cost Rate

To Whom It May Concern:

Scripps Health is not currently a direct recipient from any Federal agencies and as a result, it currently does not hold a DHHS indirect cost rate (IDC) agreement. When Scripps Health secures its first federally funded contract as a direct recipient, Scripps Health will immediately present its indirect cost rate proposal to DHHS for the purposes of negotiating an indirect cost rate. My office has internally calculated our proposed overhead rate to be 14.7% of labor (i.e. wages and benefits).

Thank you for your time.

Sincerely,

Mendy Drew

Mendy-Sue Drew, CPA, FHFMA
Director, General Accounting
Scripps Health

BUDGET JUSTIFICATION

Senior/Key Personnel

Lisa Madlensky, PhD; Consortium Co-Investigator – Effort – EFFORT **for years 1-2** % Effort **years 1-2).** Dr. Madlensky is an Assistant Professor at the Moores UCSD Cancer Center and Research Director of the UCSD Family Cancer Genetics Program. Her unique clinical and research training make her an ideal investigator for this project. Dr. Madlensky is a practicing genetic counselor (with an MSc in genetic counseling), but also has a doctoral degree in clinical epidemiology and health outcomes, as well as post-doctoral training in behavioral epidemiology. Her area of expertise is behavior change in the context of familial and genetic risk. As a scientist not directly involved in the Navigenics/Scripps Genomic Medicine project, she will provide an objective viewpoint on all analyses and interpretation. For this project, Dr. Madlensky will participate in directing analyses, interpretation of results, and writing of manuscripts.

Travel

Travel funds are requested for the study investigators to attend national scientific conferences and symposia to share findings related to the project.

Other Direct Costs

Network Communication Cost – Next Generation Network (NGN): The NGN charges cover telephone and internet costs based on a assigned cost charged monthly per FTE.

OMB Number: 0925-0001

PHS 398 Research Plan

1. Application Type:

From SF 424 (R&R) Cover Page and PHS398 Checklist. The responses provided on these pages, regarding the type of application being submitted, are repeated for your reference, as you attach the appropriate sections of the research plan.

*Type of Application:

☒ New ☐ Resubmission ☐ Renewal ☐ Continuation ☐ Revision

2. Research Plan Attachments:

Please attach applicable sections of the research plan, below.

1. Introduction to Application		Add Attachment	Delete Attachment	View Attachment
(for RESUBMISSION or REVISION only)				
2. Specific Aims	1247 Research Plan Specif	Add Attachment	Delete Attachment	View Attachment
3. Background and Significance	1248 Research Plan Backgr	Add Attachment	Delete Attachment	View Attachment
4. Preliminary Studies / Progress Report	1249-Research Plan - Prelim	Add Attachment	Delete Attachment	View Attachment
5. Research Design and Methods	1250-Research Plan - Resear	Add Attachment	Delete Attachment	View Attachment
6. Inclusion Enrollment Report	1251-Research Plan - Inclus	Add Attachment	Delete Attachment	View Attachment
7. Progress Report Publication List		Add Attachment	Delete Attachment	View Attachment

Human Subjects Sections

Attachments 8-11 apply only when you have answered "yes" to the question "are human subjects involved" on the R&R Other Project Information Form. In this case, attachments 8-11 may be required, and you are encouraged to consult the Application guide instructions and/or the specific Funding Opportunity Announcement to determine which sections must be submitted with this application.

8. Protection of Human Subjects	1252-Hum Subjects - Protect	Add Attachment	Delete Attachment	View Attachment
9. Inclusion of Women and Minorities	1253 Hum Subjects Inclusi	Add Attachment	Delete Attachment	View Attachment
10. Targeted/Planned Enrollment	1254-Hum Subjects - Targete	Add Attachment	Delete Attachment	View Attachment
11. Inclusion of Children	1255-Hum Subjects - Inclusi	Add Attachment	Delete Attachment	View Attachment

Other Research Plan Sections

12. Vertebrate Animals		Add Attachment	Delete Attachment	View Attachment
13. Select Agent Research		Add Attachment	Delete Attachment	View Attachment
14. Multiple PI Leadership Plan		Add Attachment	Delete Attachment	View Attachment
15. Consortium/Contractual Arrangements		Add Attachment	Delete Attachment	View Attachment
16. Letters of Support		Add Attachment	Delete Attachment	View Attachment
17. Resource Sharing Plan(s)		Add Attachment	Delete Attachment	View Attachment

18. Appendix Add Attachments | Remove Attachments | View Attachments

A. SPECIFIC AIMS

Over the past two years, results from several genome-wide association studies (GWAS) have emerged showcasing the discovery of specific genetic variations found to be associated with several common, complex diseases [1]. Leveraging these findings and fueled by the rapidly decreasing costs of performing genome-wide single nucleotide polymorphism (SNP) scans, a small number of companies in the United States [2, 3] and in Europe [4] have begun offering tests that aim to calculate an individual's risk for these common diseases using this genome-wide technology. These companies offer these tests, for a fee, direct-to-consumer (DTC) over the internet; that is, without the necessity of going through a medical practitioner. **While the offering of these tests – both at this stage of scientific discovery and directly to the consumer – has been the subject of much intense controversy, it is nevertheless the case that many individual consumers are purchasing these products. Despite this, however, relatively little is known about the characteristics of consumers of GWAS-based DTC personal genomics services, including why they chose to pursue this type of testing, and perhaps most critically, how they are responding to their results.** Indeed, timely answers to these questions, particularly the latter question, are critical given efforts currently underway to determine how best to regulate the sale and use of these tests [5].

The Scripps Genomic Health Initiative (SGHI) represents an opportunity to begin to address these questions. The SGHI is a large longitudinal cohort study in which participants purchase the Navigenics Health Compass DTC personal genomic risk assessment product at a discounted rate and are administered baseline (i.e., pre-risk disclosure), as well as 3- and 12-month follow-up (i.e., post-risk disclosure) web-based demographic, family medical history, and behavioral health assessments. One purpose of the study is to develop a large-scale biobank for research purposes; the other purpose, however, is to collect much needed data [6] that will allow us to begin to characterize consumers of DTC personal genomics services, as well as assess response to testing among this group of individuals. The SGHI began in October 2008, and has thus far enrolled over 4,000 individuals, the majority of whom are affiliated with the Scripps Health Hospitals and Clinics in the greater San Diego region. In addition to demographic and health history, the assessments administered also include items pertaining to attitudes about genetic testing and the perceived impact of the results, including distress related to receiving information pertaining to one's genomic risk profile. The SGHI is, to a large degree, exploratory in that it is one of the first studies to evaluate response to testing among individual consumers of DTC personal genomics services. Furthermore, although the ongoing recruitment of individuals into the SGHI is currently funded, analysis of the assessment data that is being collected is unfunded. Therefore, we are requesting two years of funding via the NIH Exploratory/Developmental Research Grant Program (R21) for analysis of these data. Our specific aims are as follows:

Specific Aim 1: Characterize consumers of DTC personal genomics services
We will (1) first compare a small number of demographic characteristics (i.e., age, gender, ethnicity, and education) for subsets of our cohort (e.g., Scripps Health Employees) between individuals who enrolled in the study relative to the broader group targeted for recruitment. We will also (2) compare data from our cohort to U.S. census data and data from other large scale population-based studies (e.g., National Health and Nutrition Examination Survey, National Health Interview Survey, California Health Interview Survey), as well as reports from research on the impact of genetic testing for single genes/mutations in single diseases on health surveillance behaviors. Finally, with respect to attitudes regarding genetic testing, we will provide descriptive data on our cohort, which is consistent with previous studies on this topic [e.g., see 7]. Specifically, we will:

a. *Demographic characteristics*. Characterize consumers with respect to age, gender, ethnicity, education, and socioeconomic status.
b. *Baseline level of genetic risk for disease*. Characterize consumers with respect to risk for common diseases based on family medical history and current health status.
c. *Behavioral health characteristics*. Characterize consumers with respect to current health screening behaviors, lifestyle characteristics (e.g., diet, exercise), and psychological functioning.
d. *Attitudes regarding genetic testing*. Characterize consumers' attitudes regarding DTC personal genomics services, including concerns about undergoing testing.

Hypotheses motivating Specific Aim 1. Based on previous studies characterizing early users of BRCA1/2 testing [8, 9], we predict that study participants (i.e., early users of DTC personal genomics services) will be younger and more likely to be of self-reported Caucasian background. We also predict that consumers will

show higher levels of baseline genetic risk for disease (i.e., based on family history assessments). We do not anticipate significant differences with respect to behavioral health characteristics, but we do predict that consumers will report few concerns regarding genetic testing and DTC personal genomics services (see *Analysis of Baseline Data* section).

Specific Aim 2: Assess response to testing among consumers of DTC personal genomics services
We will (1) assess behavioral change of all individuals in our cohort based on a comparison of assessments completed at baseline (pre-risk disclosure) versus 3- and 12-months post-risk disclosure. Change will be assessed with respect to diet, exercise, and general anxiety levels. We will further assess response to testing by (2) assessing participants' perceptions of risk, as well as the impact of obtaining their genomic risk profile. Specifically, we will:

a. *General anxiety and distress related to testing*. Assess post-risk disclosure general anxiety, as well as specific distress related to genomic risk disclosure.
b. *Perception of new disease risk*. Assess post-risk disclosure perception of disease risk, seriousness of illnesses, and confidence of participants in being able to change behavior to modify risk.
c. *Changes in health behaviors*. Assess post-risk disclosure change in health screening behaviors and lifestyle (e.g., diet, exercise).
d. *Attitudes regarding the impact of results*. Assess perceived advantages and disadvantages of receiving information pertaining to one's genomic risk profile.

Hypotheses motivating Specific Aim 2. Based on previous studies of the behavioral impact of genetic testing for single genes/mutations and single diseases such as breast cancer and colorectal cancer [10-12] we do not anticipate significant sustained changes in general anxiety post-risk disclosure, nor do we anticipate the presence of significant event-specific distress related to DTC genomic risk disclosure. We predict that participants will show wide variability in their perception of disease risk, seriousness of illnesses, and confidence in being able to change behavior to modify risk [13]. We do not predict significant changes in lifestyle (e.g., diet and exercise), although we again predict wide variability with respect to changes in health screening behaviors and perceptions regarding the impact of results.

Specific Aim 3: Evaluate potential moderators of response to testing among consumers
We will assess the extent to which certain variables may moderate behavioral and psychological response to testing. Specifically, we will examine the following variables:

a. *Demographics characteristics.* Assess the extent to which factors such as age, gender, ethnicity, education, and socioeconomic status may moderate response to testing.
b. *Perception of risk.* Assess the extent to which consumers' perception of new risk may moderate response to testing.
c. *Degree of risk.* Assess the extent to which aspects of the results profile provided to consumers (e.g., the degree of increased risk of the individual compared to the population relative risk) may moderate response to testing.
d. *Utilization of genetic counseling.* Assess the extent to which utilization of genetic counseling or consultation with one's own physician may moderate response to testing.

Hypotheses motivating Specific Aim 3. Based on previous studies of the behavioral impact of genetic testing for single genes/mutations and single diseases, we predict some degree of variation in response to testing as a function of all the variables listed above. In particular, we anticipate that individuals who utilize genetic counseling will show greater behavioral changes post-risk disclosure (i.e., over and above perception/degree of risk) relative to individuals who do not utilize counseling.

B. BACKGROUND AND SIGNIFICANCE

Over the past two years, results from several genome-wide association studies (GWAS) have emerged showcasing the discovery of specific genetic variations found to be associated with several common, complex diseases [1]. Leveraging these findings and fueled by the rapidly decreasing costs of performing genome-wide single nucleotide polymorphism (SNP) scans, a small number of companies in the United States [2, 3] and in Europe [4] have begun offering tests that aim to calculate an individual's risk for these common diseases using this genome-wide technology. These companies offer these tests, for a fee, direct-to-consumer (DTC) over the internet. The testing itself is, by definition, initiated directly by consumers, outside of a defined clinical context and, for the most part, without the involvement of a health care provider [14].

B1. Personal Genomics Services – The Controversy

The offering, directly to consumers, of genomic risk assessments based on genome-wide SNP scans has been the subject of much intense controversy [e.g., see 15]. Perhaps at the center of this controversy are the three main companies that now offer this service, 23andMe [3], deCODEme [4], and Navigenics [2]. The "personal genomics services" testing offered by these companies is distinguished from previous DTC genetic testing services (i.e., for single genes/mutations in single diseases) in that rather than focusing on selected genes or phenotypes, these tests examine, and disclose to consumers, genome-wide (> 500,000 SNPs assessed) genetic information [14] and risk estimates for more than 20 common, complex (i.e., non-Medelian inheritance pattern) diseases. This type of DTC genetic test is controversial for several reasons, including the fact that in contrast to genes implicated in Mendelian conditions, genes identified for complex diseases are associated with only modest risk, and there is a lack of research on how best to present this type of risk information to individual consumers, families, and health care providers [6].

Proponents of GWAS-based DTC genetic testing argue that there is public interest in genomic information and that it would be paternalistic to prevent individuals from accessing information about their genomes. Furthermore, these individuals propose that personal genomics services are an important means to empower consumers to make independent medical decisions, as well as an opportunity to educate consumers about their own health risks and the behavioral changes they can make to modify those risks. Proponents also argue that the absence of "perfect" risk estimates should not prohibit our healthcare system from leveraging the "incomplete" information genomics currently has to offer. On the other hand, those who are skeptical about GWAS-based DTC genetic testing note that the genome biology and science pertaining to current gene-disease risk estimates is still too unclear and that the risk estimates provided are unstable [15, 16]; given this premise, the argument is that providing these test results to individuals will have harmful effects. Specifically, individual consumers may be confused by their results, or they may be unnecessarily concerned by what are likely premature estimates of high risk, or worse yet, be falsely reassured by estimates of low risk. Opponents argue that the reporting of inaccurate or misinterpreted estimates of increased risk could result in increased anxiety and the pursuit of needless medical interventions; similar inaccurate estimates of decreased risk could result in false reassurance and failure to take appropriate preventative measures [17]. Other concerns voiced by skeptics include the possibility of discrimination and stigmatization of individuals if privacy of results is not adequately maintained. Concerns related to social costs of personal genomics services include costs associated with wasted health resources if testing routinely leads to unnecessary visits to healthcare providers (and unnecessary medical tests and procedures), as well as the possibility of the exacerbation of existing health disparities from inequitable access to these services, primarily due to cost.

B2. Controversy or no, how do consumers respond?

In a recent commentary in Nature Genetics, McBride and colleagues note that each of the arguments for and against the availability of DTC personal genomics services could be posed as research questions and testable hypotheses [6]. Indeed in drafting the current proposal, the relevant literature reviews produced several editorials, commentaries, and opinion pieces, but not a single study that presents actual data pertaining to the responses of consumers to GWAS-based DTC genetic testing. This represents an enormous gap in our current knowledge regarding an important area of public health. **In short, controversy or no, it is nevertheless the case that many individual consumers are purchasing these products. Despite this, however, relatively little is known about the characteristics of consumers of DTC personal genomics**

services, including why they chose to pursue this type of testing, and perhaps most critically, how they are responding to their results. Indeed, timely answers to these questions, particularly the latter question, are critical given efforts currently underway to determine how best to regulate the sale and use of these tests [5].

B3. Studies Underway to Close this Gap

To our knowledge, in addition to our own Scripps Genomic Health Initiative (SGHI), there are two other large-scale studies investigating the behavioral and psycho-social impacts of GWAS-based DTC genetic testing. One study is being spearheaded by the Coriell Institute and the other, termed the "Multiplex Initiative," is being spearheaded by the National Human Genome Research Institute [6]. The Coriell Institute project [18], which seeks to enroll 100,000 participants, employs an "Informed Cohort Oversight Board" (ICOB) that meets at least twice a year to review genetic variants submitted by Coriell as risk variants for health conditions. Then, only genetic variants associated with health conditions considered to be potentially medically actionable are returned to participants via a web portal that is also designed to allow participants to share their data with healthcare professionals. In parallel, the study utilizes web-based surveys to assess health and behavioral outcomes among participants. Of note, the Coriell project is currently funded through private philanthropy, foundation grants and some institutional support such that there is no cost to individual study participants; thus, although there is no doubt this study will provide critical information pertaining to the use of genomic information in healthcare, it will not provide information pertaining to *consumer* response to GWAS-based DTC genetic testing, information that is critically needed given the realities of how these tests are currently being offered to the public. The Multiplex Initiative [6], launched in 2006, aims to gain information from a population-based sample of adults about who, when offered genetic susceptibility testing for common diseases, would desire to be tested and to explore response to testing among those who opt in. Of note, however, is that the Multiplex Initiative has deployed a genetic susceptibility test prototype for 15 genetic polymorphisms associated with risk for eight common health conditions. Furthermore the study is limited to a population of individuals between 25 and 40 years of age who are all insured and are members of the same nonprofit health care organization. Thus, although this study, like the Coriell project, will also provide much needed information on individual response to testing (and certainly a major strength of this project is that it is designed to fully characterize "non-responders", or those individuals who elect not to be tested), the project also does not exactly mirror the current realities of how these tests are being offered to the public.

Significance of the Scripps Genomic Health Initiative. Like the Coriell Institute project and the Multiplex Initiative, the Scripps Genomic Health Initiative (SGHI) aims to better understand and characterize the population of individuals that elect to undergo GWAS-based DTC genetic testing, as well as assess behavioral and psychological response to testing. A major difference between the SGHI and these two other large-scale initiatives, however, pertains to the fact that the SGHI was designed to more closely resemble the realities of how these genetic tests are currently being offered to the public. Although the SGHI will be more fully described in the *Preliminary Studies* section of this proposal, an important feature of the study is that enrollment includes *actual consumers* of the Navigenics Health Compass product (although study participants do receive the product at a much discounted rate relative to the standard cost). For this reason, the SGHI would seem to be uniquely positioned to address research questions that are important for gaining information about what is actually occurring in the GWAS-based DTC genetic testing industry, but that will not be addressed by other ongoing studies.

B4. Response to Genetic Testing for Single Genes/Mutations and Single Diseases

Of note, previous studies that have examined the behavioral and psychological impacts of genetic testing and risk disclosure for single genes/mutations and single diseases such as breast cancer and colorectal cancer [10-12], have been somewhat mixed in terms of their findings. Several studies have found that risk disclosure for those individuals at higher risk (i.e., carriers of the relevant mutations) can frequently result in better adherence to recommendations regarding disease surveillance/screening [11, 19]. Some studies, however, have failed to find this effect [20], or it has been small. Similarly, findings with regard to changes in lifestyle have also been mixed [12, 21]. Previous studies have not, however, examined behavioral or psychological changes in response to GWAS-based DTC genetic testing for multiple, common diseases as we are proposing to do in the context of the SGHI.

C. PRELIMINARY STUDIES

C1. Overview of the SGHI

As previously described, the SGHI is a large longitudinal cohort study in which participants have purchased the Navigenics Health Compass product at a discounted rate and are administered baseline (i.e., pre-risk disclosure), as well as 3- and 12-month follow-up (i.e., post-risk disclosure) web-based demographic, family medical history, and behavioral health assessments. One purpose of the study is to develop a large-scale biobank for research purposes; the other purpose, however, is to collect information that will allow characterization of consumers of DTC personal genomics services, as well as assess behavioral and psychological response to testing among this group of individuals. **Overall, we aimed to design the behavioral aspect of our study based on the design of previously published studies of behavioral response to genetic testing for single genes/mutations and single diseases [12]. We have used the same or similar standardized assessments, and we will employ the same or similar statistical analysis methods. We also point out that a significant strength of our study is that it is larger than any previous published study of the behavioral impact of genetic testing of which we are aware. Furthermore, the data collection aspect of this study is fully funded; in the context of this proposal, we are requesting modest funds for analysis of the behavioral response data that is already being collected.**

C2. Methods

Recruitment. Starting in October 2008, Scripps Health employees, employee family members, employee affiliates, and Scripps Health patients were targeted for recruitment into the study. A number of strategies were used, including all-employee "email blasts", announcements via weekly informational packets (i.e., "hot sheets") and emails (i.e., "advanced notice" emails) sent to managers, announcements at system wide, quarterly manager meetings, and postings on the Scripps employee intranet (i.e., "ScrippsNet"). Recruitment and subsequent enrollment into the study is tracked, and we have included the table to the right to illustrate our methods. Specifically, the table on the right shows, for the first 4 months of the study, each recruitment strategy and the dates it was deployed.

Recruitment Method	Dates Deployed
Scripps all-employee "Email Blasts"	10/9/2008 10/21/2008 11/4/2008 12/9/2008
Manager's "Hot Sheet" announcements	10/13/2008 10/20/2008 11/3/2008 2/2/2009
Managers "Advanced Notice" email	10/8/2008- 1/6/2009
Posted on "ScrippsNet" Landing page	10/13/2008
Scripps-wide Manager's meeting announcement	10/13/2008

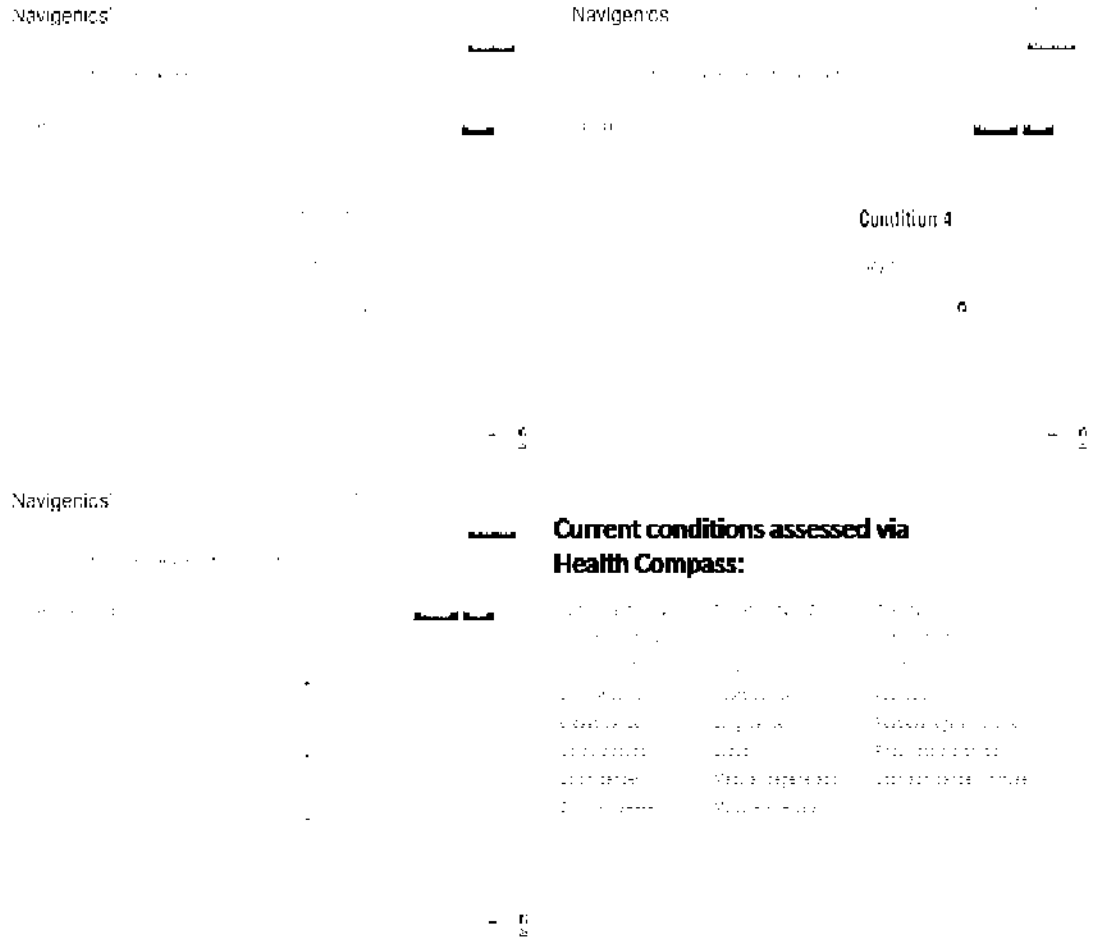
Subjects. Given that one purpose of the study is the creation of a large-scale biobank for genetic association studies, enrollment of large numbers of participants is a top priority. Thus, the inclusion criteria for the study are broad and include the following: (1) age 18 years or older; (2) able to understand and grant informed consent; (3) reliable, cooperative, and willing to comply with all protocol specified procedures; (4) able to provide payment for the Navigenics Health Compass; (5) able to complete the baseline and follow-up web-based assessments; and (6) have a valid email address. Exclusion criteria include (1) inability to provide a saliva sample. Importantly, participants in the study were offered a discounted rate for the Navigenics Health Compass product, which is normally sold by Navigenics for $2,499 (see http://www.navigenics.com/visitor/what_we_offer/our_tests/health_compass/). Specifically, our program (Scripps Genomic Medicine) subsidized this rate for SGHI participants. At study inception, the cost to participate was $150 for Scripps employees, employee family members, and Scripps patients; the cost to participate was $270 for non-Scripps affiliated individuals. Of note, however, is that the study was designed such that the cost to participate periodically increased over time. This was done to encourage potential participants to enroll early, which was done to leverage immediately available bandwidth for genotyping on the part of Affymetrix. Importantly, because of this, cost to participate will be an important covariate in most analyses of behavioral response to testing (see Research Design and Methods below). However, it should also be noted that our sample size is large enough that we will also be able to conduct analyses within groups of participants who paid the same price for the Health Compass.

Study procedures. Potential participants are directed to the Navigenics Health Compass website where they are able to read about the study, the Health Compass product, the IRB-approved Scripps informed consent, and the Navigenics User Agreement; they are also told they may ask any questions they have about the study

(prior to or after enrolling) by emailing the Scripps study coordinators. Once the informed consent process has been completed, the participant enters their payment information (i.e., for the Health Compass) and is asked to complete the web-based Baseline Health Assessment (described below). The participant is then asked to provide a 2 mL sample of their saliva, and is given two options for doing so. The participant may either have a collection kit mailed to their home, or they could choose to attend one of the scheduled saliva collection events where SGHI study coordinators provide assistance.

Navigenics. The aims of this study are to characterize consumers of DTC personal genomics services and assess response to genomic risk assessment. In this study we are specifically evaluating the Navigenics Health Compass product [2], which is one of a small number of DTC personal genomics products currently on the market. Navigenics works with Affymetrix to conduct genotyping of the samples they receive. The genotyping laboratory is a Clinical Laboratory Improvement Amendments (CLIA)-certified service laboratory where genotyping is conducted using the Affymetrix 6.0 whole-genome genotyping chip. This chip has been used in several recent GWA studies; untyped markers are imputed based on data from the HapMap.

The Health Compass. The genotype data from each individual is statistically analyzed by Navigenics to determine whether that individual carries genetic variants that increase (or decrease) susceptibility to over 20 common complex diseases (see Figure below). The algorithm used to assess risk is proprietary. The figure below depicts aspects of the Heath Compass report that is provided to each participant in our study. The report provided includes a large amount of information pertaining to risk estimates, as well as the possible "actions" one can take to modify risk (e.g., for an individual at increased risk for heart attack it is indicated that modifications in diet may serve to decrease their risk). In addition, another aspect of the report indicates the estimated lifetime risk (i.e., percentage chance a person of the same gender has of developing the condition over an average lifespan) for the individual relative to the U.S. population average. Results are also color-coded such that if the box is orange, it is a condition with respect to which the individual's estimated lifetime risk is more than 20 percent above the population average or the individual's estimated lifetime risk is higher than 25 percent (regardless of how the risk level compares to the average risk). A link to the demo (depicted in the figure above) is as follows: http://www.navigenics.com/demo/tutorial. The figure above additionally lists all of the current conditions included in the Heath Compass as of this writing.



Genetic counseling. Navigenics employs a staff of certified genetic counselors. SGHI participants are not charged for taking advantage of these services. In addition, it is Navigenics' policy to conduct "proactive outreach" (i.e., they send an email offering genetic counseling services with instructions on how to set up an appointment) to certain individuals/consumers based on their profile of genomic risk results. The criteria for doing this include any one of the following: (1) homozygous risk for Alzheimer's disease (i.e., two copies of the APOE-ε4 allele); (2) multiple sclerosis estimated lifetime risk of 1.5% or greater; (3) more than two cancers that are color coded orange (see above for explanation of color coding); (4) more than eight conditions (overall) that are color coded orange; and (5) any condition for which the individual has a greater than 60% estimated lifetime risk. As of this writing, approximately 10% of SGHI participants have engaged in genetic counseling, and as part of the study, we are tracking this on an individual level (in a way that preserves confidentiality) for inclusion of this variable in downstream analyses (i.e., see Specific Aim 3).

Study design and assessments. Our study design is such that we administer baseline (i.e., pre-risk disclosure), as well as 3- and 12-month follow-up (i.e., post-risk disclosure) web-based demographic, family medical history, and behavioral health assessments. Below is a description of these assessments, which are administered using the web-based tool, SurveyMonkey (see http://www.surveymonkey.com/Home_Landing.aspx). The baseline survey is described in detail below, and we have included our recently developed and IRB-approved 3-month survey as appendix material. Our 12-month follow-up assessment tool has not been finalized. We aim to use analyses of the baseline and 3-month data to inform possible additions to the 12-month tool, which is another reason we are requesting funding for analysis at this time.

Baseline. Our web-based baseline assessment tool was designed to assess the following general areas: (1) demographics; (2) family health-span history; (3) personal/individual health-span history; (4) health and heath screening behaviors; (5) lifestyle (operationalized to mean diet, alcohol/tobacco use, and exercise); (6) psychological functioning (operationalized to mean state and trait anxiety levels); and (7) attitudes about genetic testing. Consistent with Specific Aim 1, assessment of these general areas will allow us to characterize our cohort with respect to demographic characteristics (area 1 above), baseline level of genetic risk for disease (areas 2 and 3 above), behavioral health characteristics (areas 4, 5, and 6 above), and attitudes regarding genetic testing (area 7 above). Importantly, the selection of methods and instruments to measure these areas was based on several criteria, including the following: that the measure/method be brief; whenever possible, published; reliable and valid; and require no more than an 8th grade reading level to complete. Our general strategy was to select measures/methods that are similar to, or the same as those that have been used in previous studies that have examined the behavioral and psychological impact of genetic testing and risk disclosure for single genes/mutations and single diseases such as breast cancer and colorectal cancer [10-12]. The table on the following page depicts the content of our baseline assessment tool. Specifically, it lists the assessment areas/topics within each domain, as well as the instrument/method used to collect information pertaining to each domain. For assessment of demographics, we adapted items from the California Health Interview Survey (CHIS) [22]. For family and individual health-span history we developed items, in-house, which is consistent with the approach of a number of other studies [e.g., see 23, 24]. To assess health and health screening behaviors, we used actual items from the CHIS [22] in combination with items developed in-house. The CHIS represents the largest state health survey and one of the largest health surveys in the United States. Per their documentation, the CHIS gives health planners, policy makers, county governments, advocacy groups, and communities a detailed picture of the health and health care needs facing California's diverse population. The use of actual (as well as adapted) questionnaire items from this survey for our study is appropriate given that we are conducting the study where the majority of participants reside in Southern California. Diet is measured via The Food Screener [25], which consists of items that ask about both dietary fats, as well as intake of fruit, vegetables, fiber, and micronutrients found in fruits and vegetables. These screening instruments have been validated and found to be highly correlated with the 1995 Block 100-item Food Frequency Questionnaire [26], which has been used extensively to study individuals' dietary patterns over time. Exercise/physical activity is measured using the well-validated Godin Leisure-Time Exercise Questionnaire [27, 28]. This brief measure asks the respondent about time spent being physically active over the past 7 days, and the number of episodes of exercise is then multiplied by the relative energy expenditure in each episode. This measure has been utilized in previous longitudinal/intervention studies [29-31]. General state and trait anxiety is assessed using the well-validated and widely-used Spielberger State-Trait Anxiety Inventory (STAI) [32], which, per a recent review of studies that have examined the psychological and behavioral impacts of genetic testing [12], has been used in the majority of these studies to measure

BASELINE ASSESSMENT DOMAINS		
Domain	**Assessment Sub-domains**	**Instrument/Method Used**
Demographics	**Personal demographics** (a) Items including gender, birth year, ethnicity, household income, education level, occupation, primary language spoken in home, family geographic region of origin	•items adapted from CHIS 2007 Adult Questionnaire
Baseline Disease Risk	**Family health-span history** (a) Immediate family ages, age at death, and cause of death (b) Immediate and extended family history of: •Heart-related health problems (10 specific conditions) •Cancer-related health problems (15 specific cancers) •Neurological/mental health-related problems (15 specific conditions) •Breathing-related health problems (4 specific conditions) •Other health problems (10 specific conditions)	•questionnaire developed in-house
	Personal/individual health-span history (a) Developmental history •Birth complications •Medical problems in first year of life •Hand dominance (proxy for early CNS anomalies) (b) Individual health history of: •Heart-related health problems (10 specific conditions) •Cancer-related health problems (15 specific cancers) •Neurological/mental health-related problems (14 specific conditions) •Breathing-related health problems (4 specific conditions) •Other health problems (10 specific conditions) (c) Individual heath history of allergies (6 specific conditions) (d) Current prescription medications (e) Current vitamin/nutritional supplements (f) Current height and weight (g) Assessment of ability to complete activities of daily living	•questionnaire developed in-house
Behavioral Health Characteristics	**Health screening behaviors** (a) Heath care utilization •Frequency and time since seeing a medical doctor •Time since seeing an alternate health care professional •Time since specific selected screening/surveillance procedures (9 specific procedures) (b) Possession of health insurance (c) Own perception of health (good, very good, etc.)	•items from CHIS 2007 Adult Questionnaire •questionnaire developed in house
	Diet (a) Own perception of eating habits (b) Fat, fruit, vegetable, and fiber intake	•The Food Screener (Block et al., 2000) •items developed in-house
	Alcohol/tobacco use (a) Current/past drinker (b) Current/past user of tobacco products (c) Duration and frequency of use (alcohol and tobacco)	•items developed in-house
	Exercise (a) Physical activity during typical 7-day period •Strenuous exercise (frequency and duration) •Moderate exercise (frequency and duration) •Mild exercise (frequency and duration)	•Godin Leisure-Time Exercise Questionnaire (Godin & Shephard, 1985)
	Psychological functioning (a) State anxiety (b) Trait anxiety	•Spielberger State-Trait Anxiety Inventory (Spielberger, 1983)
Attitudes About Genetic Testing	**Perception of genetic testing** (a) Concerns about participation in study (b) Value of genetic testing (c) Predicted impact of high/low risk results	•items developed in-house

anxiety pre- and post-genetic risk disclosure for single genes/mutations in single diseases. Finally, we have used items developed in-house to assess attitudes surrounding DTC personal genomics services. In the *Analysis of Baseline Data* section of the proposal (below) we present analysis of a subset of these items.

3-month follow-up. In the context of our 3-month follow-up assessment (which is finalized and will be administered in June 2009) we ask about any changes in the participant's individual health status with respect to all the conditions initially assessed at baseline (e.g., "Have you developed or been diagnosed with any of the following heart-related health issues that you did not have at the time of the initial survey?"). We also ask about changes with respect to current medications, vitamin/supplement use, and height and weight. We ask about any changes made to health insurance, life insurance, or long-term care/disability insurance. We assess actual changes, post-risk disclosure, to the frequency of health screening behaviors (i.e., all behaviors assessed at baseline), as well as the participant's *intention* to engage in each screening behavior post-risk disclosure. We also assess changes to alcohol/tobacco use via two items pertaining to each area (e.g., "Since receiving your genetic test results, have you made any changes to your pattern of tobacco use?" and "If yes, please specify how your pattern of use has changed since receiving your genetic test results"; the participant can choose from 6 responses, including "quit using", "decreased use significantly", decreased use slightly", "increased use slightly", "increased use significantly", "started using"). Further, our standardized measures of diet (The Food Screener) [25], exercise (Godin Leisure-Time Exercise Questionnaire) [28], and general state/trait anxiety (STAI) [32] are all re-administered at the 3-month follow-up to assess change in these areas post-risk disclosure. We also ask several questions with respect to the participants' use/reading/viewing of the Health Compass report provided by Navigenics (described above). In addition to re-assessment of domains measured at baseline, we also assess a number of new areas (see table above), including event-specific distress, with the event being genomic risk-disclosure. For this we administer the Impact of Events Scale-Revised (IES-R) [33, 34]. The IES-R is a widely used self-report measure in the field of traumatic stress, and more specifically, has also been successfully used to assess the impact of genotype disclosure in previous genetic testing studies [e.g., see 35, 36]. In addition, for the condition the participant is most concerned about post-risk disclosure (i.e., we ask "Since receiving your genetic test results, what are the top three medical conditions, of those assessed, you are MOST concerned about?") we assess illness perceptions, as well as perceived ability to modify risk (i.e., "perceived control") via methods adapted from Claes and colleagues' study of response to testing for hereditary nonpolyposis colorectal cancer [11]; based on methods from this study we also assess the perceived impact of genomic risk disclosure. Perceived seriousness of the condition the person is most concerned about is assessed with a 12-item scale adopted from Champion [13]. Finally, utilization of genetic counseling services, as well as the extent to which the participant discussed their results with their physician or healthcare provider (and whether nor not the provider ordered any medical tests/procedures based on the results), is assessed via several items developed in-house.

3-MONTH FOLLOW-UP: ADDITIONAL ASSESSMENT DOMAINS

Domain	Assessment Sub-domains	Instrument/Method Used
Event-specific Distress	**Impact of Genomic Risk Disclosure** (a) Intrusion (b) Avoidance (c) Hyperarousal	•Impact of Events Scale-Revised (Weiss & Marmar, 1997)
Illness Perceptions	**Subjective Risk Perception** (a) Perceived risk before and after risk disclosure	•Based on method in Claes et al., 2005
	Perceived Seriousness of Illness (a) Seriousness of condition that is most concerning	•scale adopted from Health Belief Model Instrument (Champion, 1984)
	Perceived Ability to Modify Risk (a) Confidence in "actionability" of disease via health screening (b) Confidence in "actionability" of disease via changes in diet, exercise, etc.	•Based on method in Claes et al., 2005
Perceived Impact	**Perceived Impact of Genomic Risk Disclosure** (a) Advantages (b) Disadvantages	•Based on method in Claes et al., 2005
Utilization of Counseling	**Utilization of Genetic Counseling Services** (a) Utilize Navigenics Genetic Counselor (b) Utilize physician or other heathcare provider	•items developed in-house

12-month follow-up. In the context of our 12-month follow-up assessment (which is not yet finalized and will be administered in March 2010), we will again re-assess most domains and re-administer all of our standardized measures. In addition, we plan to add measures to further assess our participants' reasons for participation and "adoption" of DTC personal genomics services. Specifically, diffusion of innovations theory has been used to explain the spread of new ideas and practices [37], and evidence suggests that it may help explain human behavior and provide a guide for the design of interventions to change behavior. A recent study evaluated components of diffusion theory with respect to women who were "early adopters" of BRCA1/2 testing [8]. At our 12-month assessment we will incorporate measures from this study into our study. Specifically, we will assess participants' attitudes and perceptions about the relative advantage, complexity, and compatibility of DTC personal genomics services, as well as the level of innovativeness of participants' within the medical domain. This will be done using standardized measures commonly used in the diffusion theory literature [38-40]. See table to the right for an overview of the primary domains assessed at each study time-point. Of note, because the 12-month assessment tool has not yet been finalized, we plan to leverage our preliminary studies, as well as new studies on this topic that may emerge in the literature, in determining whether inclusion of other assessment domains/items may be warranted at this time-point.

Domain	Base-line	3-Month	12-Month
Demographics	x		
Family health-span history	x		
Individual health-span history	x	x	x
Heath screening behaviors	x	x	x
Alcohol/tobacco use	x	x	x
Diet	x	x	x
Exercise	x	x	x
Psychological functioning	x	x	x
Perception of genetic testing	x	x	x
Event-specific distress		x	x
Perceived susceptibility		x	x
Perceived seriousness		x	x
Perceived control		x	x
Perceived impact		x	x
Utilization of counseling		x	x
Compatibility (Diffusion Theory)			x
Complexity (Diffusion Theory)			x
Relative advantage (Diffusion)			x
Domain-specific innovativeness			x
Additional to-be-determined**			x

Steps to minimize threats to validity. We note that designs without control groups, such as our one-group pretest-posttest design, can yield strong causal inferences by minimizing threats to validity (i.e., by reducing the plausibility of alternative explanations for the "treatment effect") [41]. For instance, with the current design, the primary threats of concern are as follows: (1) maturation and history – natural changes or "outside" changes that could mimic an effect of genomic risk disclosure; (2) testing – in this case exposure to the baseline assessment could produce changes that could mimic a treatment effect; and (3) attrition – loss of subjects to measurement, i.e., individuals who do not complete the 3- or 12-month follow-up assessments, which could produce confounds if that loss is systematically correlated with study variables. Shadish and colleagues (2002) recommend minimizing these threats and improving this design by adding a "nonequivalent dependent variable", which is diagrammed below. In this scheme, Measures A and B are similar constructs. Measure A (outcome) is expected to change because of treatment.

One-Group Pretest-Posttest Design:
$O_1 \; X \; O_2$

Addition of a Nonequivalent Dependent Variable:
$\{O_{1A\text{Perceived Risk of Navigenics Cond.}}, O_{1B\text{Perceived Risk of Parkinson's}}\} \; X \; \{O_{1A\text{Perceived Risk of Navigenics Cond.}}, O_{1B\text{Perceived Risk of Parkinson's}}\}$

Measure B (the nonequivalent dependent variable) is not; however, Measure B is expected to respond to the salient internal validity threats in the same way as Measure A. In the current study, we implemented the use of non-equivalent dependent variables in several instances. One example of this is that we included items on our assessment measure that assess changes in perceived risk among consumers for conditions reported on in the Navigenics Health Compass (i.e., Measure A, the outcome), as well as Parkinson's disease, a condition that is not reported on by Navigenics (Measure B, which should respond to internal validity threats in the same way as our outcome). We will closely assess our results across our nonequivalent dependent variables in an effort to identify any validity threats to our study.

Strengths of the SGHI. We note several strengths of the SGHI, most notably the (1) large sample size (anticipated total enrollment of ~5,000 individuals); (2) the fact that recruitment, enrollment, and data collection are already funded and nearly complete (i.e., we are requesting only modest funds for analysis of existing data); (3) the fact that the research aims of the study are of high priority to the NHGRI as evidenced by recent RFAs; and (4) the research environment and team of multidisciplinary investigators who will execute the proposed work. Along these lines, we emphasize another strength of the study, which is that we have

attempted to put in place several safeguards to ensure that the proposed work will be free from bias that could stem from conflicts of interest. **Specifically, no one affiliated with Navigenics or Affymetrix will be directly involved in the data analysis outlined in this proposal, and we also have the pledged written support of both companies (see letter of support from Vance Vanier, M.D., Chief Medical Officer, Navigenics and letter of support from Rob Lipshutz, Ph.D., Senior Vice President, Affymetrix) in completing these studies and publishing the results – irrespective of the nature of the findings.** Furthermore, Dr. Lisa Madlensky, Ph.D., University of California, San Diego faculty member, practicing genetic counselor, and health behavior researcher, has joined our research team as an "objective" co-investigator who has not been involved in the development of the project up to now, and has no current or previous ties with Navigenics, Scripps Health, or any other DTC genetic testing entity. Thus, although as with any study the SGHI has some limitations (e.g., our use of relatively brief behavioral assessment tools, our one-group pretest-posttest design, the demographic make-up of our sample does not reflect the general population), we believe the strengths of the study significantly outweigh these limitations, and as such, deployment of modest funds for analysis of SGHI data would have a favorable cost/benefit ratio.

C3. Analysis of Baseline Data

Recruitment and enrollment into the SGHI began in October of 2008, and as of this writing, we have enrolled a total of 4,396 participants; enrollment will remain open until September 30, 2009. We recently received baseline assessment data for the first N = 2,779 participants, and what follows are some preliminary analyses of those data. Since we have not yet administered our 3-month follow-up assessment, no preliminary follow-up data are available at this time.

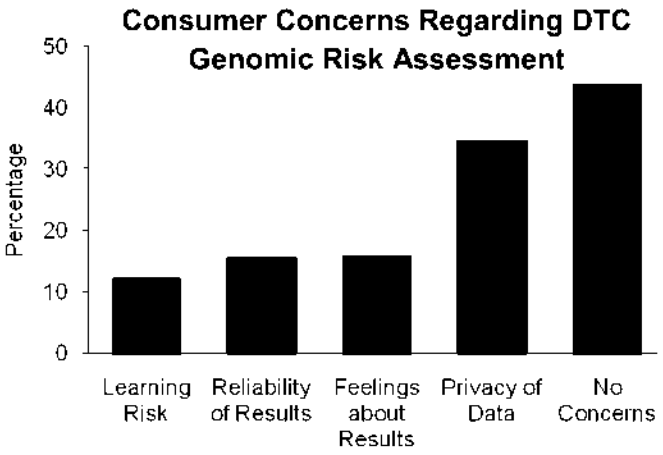
Study sub-groups and demographic comparison to "nonresponders". Via agreements between SGHI principal investigator Eric J. Topol, M.D. and community business leaders, targeted recruitment of participants has occurred at various companies and organizations in addition to Scripps Health. To show this, the table to the left depicts "participant type" for our first 2,779 enrollees. As shown, the majority of our participants are either Scripps Health employees (n = 960) or are affiliated with Scripps in some other way (e.g., family member of employee, patient, etc.). We hypothesized that the demographic make-up of each sub-group of study participants would vary, and thus conducted separate analyses of demographic data within four of our subgroups (i.e., the four with the largest N). As shown in the table below, although on average SGHI participants are predominantly Caucasian, female, have a 4-year college degree, a household income of 100 – 150k per year, and an average age of 46 years, demographic characteristics do vary as a function of participant type. Thus, with respect to some analyses we will either conduct separate analyses within each subgroup, or use participant type as a covariate in analyses examining the behavioral and psychological response to testing. For a second analysis, we acquired access to basic demographic data for all Scripps Health employees (see http://money.cnn.com/magazines/fortune/bestcompanies/2009/ snapshots/59.html). From these data, we discovered that as a group, Scripps Health Employees (the "denominator" of our Scripps Health Employee participant sub-group) are 49% Caucasian and 78% female. Our study sub-group, however, is 78% Caucasian and 76% female (see table to the right). This very basic finding suggests that among Scripps Health Employees, Caucasian individuals were more likely to enroll into the SGHI, which may have implications with respect to demographic groups that may be more likely to "adopt" DTC personal genomics services (or this may reflect well-known tendencies of different demographic groups to participate in any type of research). This finding is also

Type of Participant	N	% of Total
Scripps Health employee	960	34.5
Scripps Health employee family	468	16.8
Scripps Health friend	482	17.3
Scripps Health patient	128	4.6
Microsoft employee	521	18.7
Microsoft friend or family	168	6.0
Affymetrix employee	25	0.9
Affymetrix friend or family	27	1.0
TOTAL	**2,779**	**100**

Variable	Scripps Health Employee	Scripps Health Employee Family	Scripps Health Friend	Microsoft Employee	Total Sample
Sample Size	960	468	482	521	2779
Age	46.8 (11.8)	48.7 (14.6)	48.9 (14.0)	40.5 (8.6)	46.5 (12.7)
Gender (% Female)	75.8%	50.6%	49.2%	27.3%	56.1%
Ethnicity (% Caucasian)	78.5%	85.5%	93.1%	81.2%	83.9%
Education (modal)	4-year coll. degree	4-year coll. degree	Master's degree	4-year coll. degree	4-year coll. degree
Income (modal)	50–100k/yr	100–150k/yr	50–100k/yr	100–150k/yr	100–150k/yr

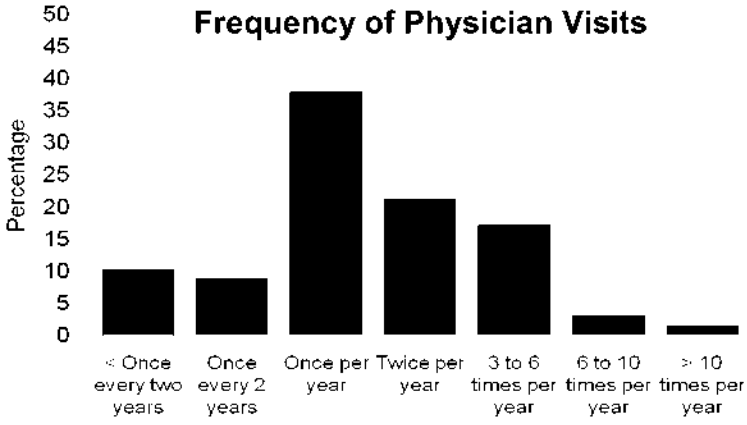
consistent with previous studies characterizing early users of BRCA1/2 testing [8, 9], which found that early users were more likely to be self-reported Caucasian.

Consumer perceptions of DTC genomic risk assessment. We recently assessed available baseline data with respect to study participants' perceptions of DTC genetic testing (Bloss et al., submitted). Demographic characteristics for the N = 2,779 individuals are listed above. Specifically, participants were asked about their perceptions of DTC genetic testing and to report any concerns they had about participating in the study [42]. An individual could endorse multiple answers, and responses for the group as a whole are depicted in the figure to the right: 12.2% endorsed concerns related to learning about their disease risk; 15.5% concerns related to the quality and reliability of the results; 15.9% concerns related to not knowing how they would feel about their results; 34.7% concerns related to privacy issues about their data; and 43.8% indicated no concerns. Separate logistic regressions of each of these variables on gender, age, income, and education were conducted. Gender and age were significant predictors of concerns related to learning about disease risk and concerns related to not knowing how they would feel about the results; specifically, younger individuals and women were more likely to endorse these concerns. Younger age was associated with endorsing concerns related to the quality and reliability of the results, and younger age and higher education were both associated with concerns related to privacy issues. Finally, older age, higher income, and lower education were all associated with endorsing no concerns. Although these effects were statistically significant, effect sizes were small. The table below depicts the percentages of individuals endorsing these concerns within each study sub-group and within gender. These findings suggest that concerns among consumers of DTC personalized genomics services may vary as a function of demographics.



Cohort	Gender	Concerns related to learning about my disease risk from my DNA testing	Concerns related to the quality and reliability of the testing lab and the results	Concerns related to not knowing how I will feel about my results	Concerns related to potential privacy issues about my data	I do not have concerns about participating in this initiative
Scripps Health N=1,910	Men	9.5	11.2	12.1	32.4	51.2
	Women	15.1	51.1	19.3	33.6	45.3
Microsoft Employee N=521	Men	8.1	26.0	12.5	44.4	35.0
	Women	16.9	18.3	23.9	40.1	36.6
Total Sample N=2,779	Men	9.5	16.2	12.4	36.8	45.8
	Women	14.7	15.7	19.2	34.7	44.4

Health behaviors among consumers of DTC genomic risk assessment. Finally, in another preliminary analysis of available baseline data, we examined the extent to which individuals in our sample reported having health insurance, as well as the frequency of self-reported physician visits. Analyses indicated that the vast majority of participants reported having health insurance (98.8%) and most reported visiting their physician once (37.9%) or twice (21.2%) per year [42]. These results are depicted in the figure to the right. Health behavior statistics like this, as well as other screening behaviors (e.g., frequency of mammograms) will be compared to data from population-based heath studies (e.g., California Health Interview Survey), as well as reports from research on the impact of genetic testing for single genes/mutations in single diseases.



D. RESEARCH DESIGN AND METHODS

Below we provide an overview of our analysis methods pertaining to each of our specific aims. We point out, however, that the overall design of the SGHI was described above, and much of our general approach to analysis of these data was illustrated in the *Analysis of Baseline Data* section above. In addition, an important overall consideration in the analysis of data from our study is the issue of attrition. Studies employing internet-based survey and intervention methods suggest that we can expect attrition rates of between 20% and 30% [43, 44]. This is coupled with the likely loss of some proportion of the data in the process of data cleaning due to missingness, exclusions based on validity checks (as outlined in *Steps to minimize threats to validity*, above), outliers, and other reasons. Thus, we estimate that approximately 75% of our total projected sample (~ N = 5,000 participants) will ultimately have complete data, which leaves approximately 3,750 individuals. Thus, all power calculations presented below are based on this number. Furthermore, we will also examine attrition by filling in missing follow-up "change" scores with baseline values and conducting conservative "intention-to-treat" analyses.

D1. Specific Aim 1: Characterize consumers of DTC personal genomics services

Approach. We will (1) first compare a small number of demographic characteristics (i.e., age, gender, ethnicity, and education) for subsets of our cohort (e.g., Scripps Health Employees) between individuals who enrolled in the study relative to the broader group targeted for recruitment. We show an example of this for our Scripps Health Employee subgroup in the *Analysis of Baseline Data section.* We will also (2) compare data from our cohort to U.S. census data and data from other large scale population-based studies (e.g., National Health and Nutrition Examination Survey, National Health Interview Survey, California Health Interview Survey). Finally, with respect to attitudes regarding genetic testing, we will provide descriptive data on our cohort, which is consistent with previous studies on this topic [e.g., see 7].

Outcome variables and analysis. Among our variables of interest are (a) demographic characteristics (i.e., age, gender, ethnicity, education, and socioeconomic status), (b) baseline level of genetic risk for disease (i.e., consumers' responses to our family health-span history questionnaire, which pertains to family history of several common, complex diseases), (c) behavioral health characteristics (i.e., current health screening behaviors, diet, exercise, as well as psychological functioning), and (d) attitudes/concerns regarding DTC personal genomics services. Statistical methods for this aim will primarily involve basic descriptive procedures, some of which are illustrated above.

D2. Specific Aim 2: Assess response to testing among consumers of DTC personal genomics services

Approach. We will (1) assess behavioral change of all individuals in our cohort based on a comparison of assessments completed at baseline (pre-risk disclosure) versus 3- and 12-months post-risk disclosure. Change will be assessed with respect to diet, exercise, and general anxiety levels. We will further assess response to testing by (2) assessing participants' perceptions of risk, as well as the impact of obtaining their genomic risk profile.

Outcome variables and analysis. Among our variables of interest are (a) general anxiety and distress related to testing (i.e., scores on the STAI and IES-R), (b) perception of new disease risk (i.e., responses to assessment items pertaining to perception of disease risk, seriousness of illnesses, and confidence of participants in being able to change behavior to modify risk), (c) health behaviors post-risk disclosure (i.e., scores on the Food Screener and Godin exercise questionnaire and assessment items pertaining to health surveillance behaviors), (d) consumer responses regarding the impact of receiving their results (i.e., consumer-reported advantages and disadvantages). Statistical methods for this aim will generally be as follows: Generally, for assessment of change we will draw on methods from the clinical intervention and treatment outcome literature where importance is placed on identifying change from baseline to post-intervention. Depending on the nature of the data being analyzed (e.g., count, interval), we will identify the most appropriate analytic approach for determining statistical significance (i.e., whether there has been a statistically significant change in any given behavioral outcome).

In addition to statistical significance, the clinical intervention and treatment outcome literature also places importance on identifying clinically important intra-individual change from pre- to post-intervention. We will thus follow suit in our study and will assess (in addition to statistically significant change), clinically meaningful change whenever possible. With respect to assessment of clinically significant change, we will specifically utilize two accepted methods for this, including (a) the Individual Effect Size assessment and (b) the Reliable Change Index. The Individual Effect Size method has been widely used for classifying both group and individual patient change [e.g., see 45, 46]. With this method, differences between pre-treatment and post-treatment scores can be standardized to quantify an intervention's effect in units of standard deviation (SD), which therefore yields a number that is independent of measuring units and can be used to compare magnitude of treatment outcomes. In addition to the Individual Effect Size method, we will also employ the widely used Reliable Change Index [47]. The Reliable Change Index is similar to the effect size statistic in that it calculates mean differences between pre-treatment and post-treatment scores, but it divides the difference by a standard error of the measure (e.g., State-Trait Anxiety Inventory) that includes not only the standard deviation of baseline scores, but also the reliability coefficient of the measure itself that is being used to assess the construct under study. Reliable Change Index values are then referenced to the normal distribution, and values that exceed 1.96 are interpreted as being unlikely ($p < 0.05$) unless an actual and reliable change has occurred [48]. In short, these two methods have been developed for assessment of intra-individual change between pre- and post-treatment assessment and are thus highly appropriate and applicable to our study.

Specific outcomes and specific diseases. We will also conduct planned analyses according to disease. That is, for some conditions (e.g., obesity, diabetes, cardiovascular disease) there are multiple behaviors of interest with specific "guidelines" in terms of behavioral changes/modifications that can be made (e.g., diet changes, increased exercise, cholesterol tests); for others, however, guidelines are less clear (e.g., lupus, multiple sclerosis, Crohn's disease). Similarly, for some conditions there are clear health screening behaviors that are being assessed (e.g., breast cancer, prostate cancer), but for others, there are not.

Statistical power. We will assess statistical significance of changes in our behavioral measures of interest, via a paired-samples t-test or a Wilcoxon signed rank test depending on how the data are found to be distributed. The paired-samples t-test compares the means of two quantitative variables for a single group (e.g., mean values for a variable that is measured on the same individuals before and after an intervention); the Wilcoxon signed rank test is essentially the non-parametric version of the paired-samples t-test. For example, in the case of exercise, we will compare mean total scores on the Godin Exercise Questionnaire at baseline and at follow-up. Although our study is larger than any previous study of which we are aware looking at the behavioral impacts of genetic testing [12], we have calculated statistical power for our analyses based on our study parameters. The table to the left shows the results of a power analysis for our paired-samples t-test based on n = 3,750 individuals and a conservative alpha level of 0.01 (note that depending on the total number of behavioral change areas we examine, we will employ conservative Bonferroni-corrected alpha levels). In the table to the left, we have shown the power we will have to detect effect sizes of varying magnitudes. We utilized the t-test module in the G*Power 3.0 software [49] to carry out these calculations, specifically employing the difference between two dependent means (i.e., matched pairs) test. As shown, we have good power to detect even very small effects (~.06). When data are available from our 12-month follow-up assessment, we will employ appropriate longitudinal methods, including repeated measures Analysis of Variance (ANOVA) with post-hoc simple effects tests.

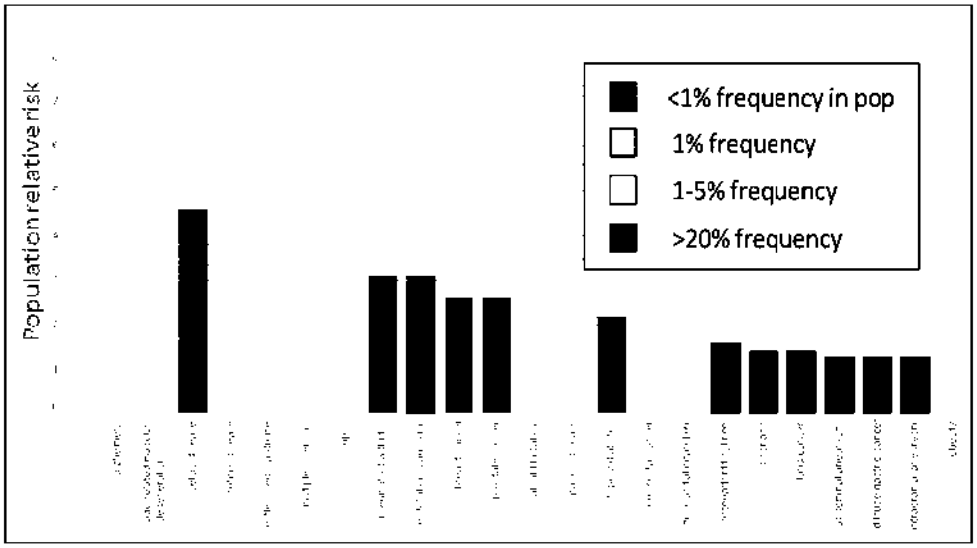
Effect Size: Paired samples t-test	Power
.05	0.686
.06	0.864
.07	0.956
.08	0.999
.09	1.0
.10	1.0

D3. Specific Aim 3: Evaluate potential moderators of response to testing among consumers

Approach. We will assess the extent to which certain variables may moderate behavioral and psychological response to testing.

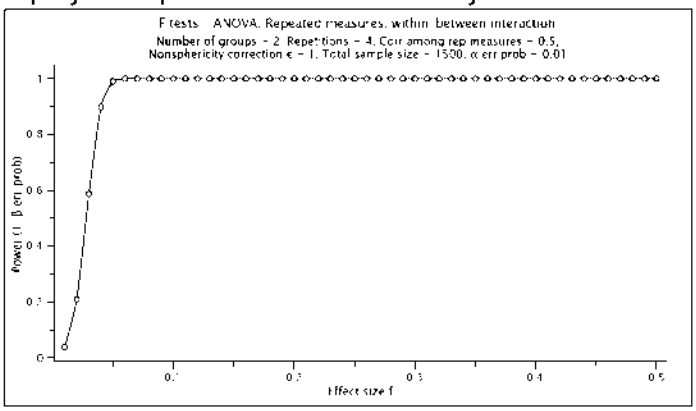
Outcome variables and analysis. We will examine the extent to which (a) demographic characteristics, (b) perception of new disease risk, (c) degree of risk reported to consumers, and (d) utilization of genetic counseling services moderate response to testing. To illustrate this using the degree of risk reported to consumers, we first show the frequency of observing, in the population, maximum genetic risk for each

condition assessed (personal communication, April 29, 2009, Michelle Cargill, Ph.D., Navigenics). See figure to the right. To explain how this figure should be interpreted, we will use Alzheimer's disease (AD) as an example. As can be seen from the figure, the maximum genetic risk that can be identified/reported with the Navigenics Health Compass product is a population relative risk of ~8.5, which means that an individual in this highest risk "bin" for AD is reported to have an 8.5-fold higher risk of developing the disease than the average population genetic risk. Furthermore, the AD bar is coded yellow, which means that the number of people in the population with this level of risk is 1-5%. If we round this up to 5%, this would suggest that in our sample of N = 3,750 individuals, approximately 150 individuals would fall into this highest risk bin for AD. In the table to the right, we show these sample size calculations for each level of frequency.



Frequency	N in our Sample of 3,000	Number of Conditions with that Frequency
<1% (.05%)	18	5 out of 23 total
1%	37	2 out of 23 total
1-5% (5%)	187	9 out of 23 total
>20% (20%)	750	7 out of 23 total

Statistical power. As an example of how we will approach these analyses, we will identify individuals in the highest risk bin (as shown above), as well as age-, gender-, and education-matched individuals in the lowest risk bins and evaluate the extent to which each group differentially endorses behavioral and psychological changes post- risk disclosure. For analysis of outcome data based on our standardized instruments we will employ a repeated measures analysis of variance (ANOVA). In this analysis, time will be the within subjects factor and risk (i.e., high versus low) the between subjects factor. To test our hypothesis, we will examine the interaction between time and risk group. Please see figure to the right, which depicts our power for assessing this interaction in a group of 1,500 individuals (i.e., n = 750 in each group) with an alpha level of 0.01. Of note is that this constitutes only one of the approaches we will take to examining "degree of risk reported" as a moderator of response to testing.



D4. Exploratory Aims/Analyses

Given that the R21 mechanism is geared toward exploratory studies, we propose to conduct some exploratory analyses, in addition to those embodied in the aims we have already articulated. These analyses may include (but will likely not be limited to) (1) analyses centered around the risk estimates that are provided for multiple conditions, and (2) data mining to determine if there are "case-specific" findings of interest. Pertaining to (1) above, we will create a composite risk measure (e.g., a measure that represents the number of conditions with increased risk minus the number of conditions with decreased risk) and assess the extent to which participants with an overall increased risk show unique behavioral and psychological profiles (e.g., higher post-risk disclosure distress measures). Such an analysis is uniquely relevant to GWAS-based DTC genetic testing where multiple conditions are being assessed simultaneously. Pertaining to (2) above, we will conduct data mining to determine whether there are any "case findings" of individuals who report decreases in, e.g., health screening behaviors or high levels of reassurance (i.e., low anxiety) after getting a "decreased risk report", but are actually at high risk based on family history, personal heath history, or other risk factors. This is an issue that commonly arises in commentaries on GWAS-based DTC genetic risk testing, and as such, would be important to assess in our data.

D5. Timeline

To the right, we outline the deliverables and time frame for the proposed work. The timeline is broken down by three-month interval (quarter) within each year: Q1 (April-June), Q2 (July-September), Q3 (October-December), Q4 (January-March), respectively.

Study Procedure	Year 1 4/1/2010-3/31/2011				Year 2 4/1/2011-3/31/2012			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Progress Reports	X	X	X	X	X	X	X	X
Analysis of Baseline and 3-month follow-up data	X	X	X					
Construction of 12-month follow-up assessment	X							
Deployment of 12-month follow-up assessment	X	X	X					
Manuscript Preparation (baseline and 3-month)			X	X	X			
Analysis of 12-month data				X	X	X		
Manuscript Preparation (baseline, 3-month, and 12-month)						X	X	X

Inclusion Enrollment Report

This report format should NOT be used for data collection from study participants.

Study Title: Response to Testing Among Consumers of DTC Personal Genomics Services

Total Enrollment: 2,779 (avail. data) 4,396 (total) **Protocol Number:** IRB: HSC 08-5069

Grant Number: N/A Clinical Trials: NCT00808587

PART A. TOTAL ENROLLMENT REPORT: Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race

Ethnic Category	Sex/Gender			
	Females	Males	Unknown or Not Reported	Total
Hispanic or Latino	113	47	0	160 **
Not Hispanic or Latino	1447	1098	0	2545
Unknown (individuals not reporting ethnicity)	0	0	74	74
Ethnic Category: Total of All Subjects*	1560	1145	74	2779 *
Racial Categories				
American Indian/Alaska Native	5	1	0	6
Asian	111	95	0	206
Native Hawaiian or Other Pacific Islander	18	4	0	22
Black or African American	20	22	0	42
White	1406	1023	0	2429
More Than One Race	0	0	0	0
Unknown or Not Reported	0	0	74	74
Racial Categories: Total of All Subjects*	1560	1145	74	2779 *

PART B. HISPANIC ENROLLMENT REPORT: Number of Hispanics or Latinos Enrolled to Date (Cumulative)

Racial Categories	Females	Males	Unknown or Not Reported	Total
American Indian or Alaska Native	0	0	0	0
Asian	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	0	0	0	0
White	113	47	0	160
More Than One Race	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of Hispanics or Latinos**	113	47	0	160 **

* These totals must agree.
** These totals must agree.

PROTECTION OF HUMAN SUBJECTS

1. RISK TO SUBJECTS

Human Subject Involvement

The current proposed work will leverage data collected as part of the Scripps Genomic Health Initiative (SGHI), which is an ongoing, Scripps IRB-approved, longitudinal cohort study of over 4,000 individuals that began in October 2008. Initial recruitment efforts for the SGHI were focused on the Scripps Health community and included Scripps Health employees, employee family members, employee "friends" or affiliates, and Scripps Health patients. More recently, via agreements between SGHI principal investigator Eric J. Topol, M.D. and community business leaders, targeted recruitment of participants has occurred at various companies and organizations in addition to Scripps Health, including Microsoft, Qualcomm, and Sempra among others; recruitment efforts have also focused on members of the general public. The current proposal is limited to analysis of data that is already being collected as part of the SGHI. The inclusion criteria for the SGHI are as follows: (1) age 18 years or older; (2) able to understand and grant informed consent; (3) reliable, cooperative, and willing to comply with all protocol specified procedures; (4) able to provide payment for the Navigenics Health Compass; (5) able to complete the baseline and follow-up web-based assessments; and (6) have a valid email address. Exclusion criteria include (1) inability to provide a saliva sample.

Consent

The IRB-approved electronic consent form includes details of study procedures, as well as the potential risks of participating in the study. The consent includes both the Scripps consent form, as well as the Navigenics User Agreement, both of which have been reviewed and approved by the Scripps IRB. Enrollment into the study proceeds as follows: Potential participants are directed to the Navigenics Health Compass website where they are able to read about the study, the Health Compass product, the Scripps informed consent, and the Navigenics User Agreement; they are also told they may ask any questions they may have about the study (prior to or after enrolling) by emailing the Scripps study coordinators at SGHI@scrippshealth.org. If the potential participant chooses to enroll, once the informed consent has been electronically signed, the participant can print out the informed consent for their personal records. After providing the discounted payment for the Health Compass product, the participant is then asked to provide a 2 mL sample of their saliva, and is given two options for doing so. The participant may either have a collection kit mailed to their home or they can choose to attend one of the scheduled saliva collection events where SGHI study coordinators provide assistance with sample collection. The informed consent was approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB). The principles of informed consent are implemented according to the current revision of the Declaration of Helsinki, the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), and other applicable regulatory requirements.

Importantly, participants may withdraw/discontinue from the study at their own choice at any time without giving a reason, at which time his/her DNA sample will be destroyed. In order to withdraw from the study, the participant is told to contact the member services/customer service number provided on the Navigenics website as well as on their informed consent. Navigenics will delete the subject's data and their phenotype information from all operational Navigenics systems, and their genetic data and phenotype information will not be included in any future archive of these systems unless Navigenics is required by applicable law to retain any such data and information, in which case Navigenics will do so only for so long as required, and only for the purposes of such laws.

Confidentiality

Confidentiality of all study participants is emphasized and protected through the issuance of a unique identification number, which is used among the collaborating institutions to identify participants, biologic specimens, and data. This de-identified unique identifier is also used in analysis of the behavioral data, which does not include any other identifying information. Participant data are kept in a secure database at the Scripps Translational Science Institute (STSI). This database is protected such that only authorized study personnel are allowed to look at this information. The de-identified data is accessible via a secure server with maximum electronic security measures. STSI and Navigenics have the information that

matches the unique identification number with traditionally used identifying information, such as the participant's name, address and phone number. These entities keep the information that matches the code to this traditionally used identifying information in a secure database. All other researchers and personnel, including those who will be working with participants' saliva samples and medical information do not have access to any of the traditionally-used identifying information for participants. Finally, Navigenics receives all genotyping data from Affymetrix, a CLIA certified service laboratory. All participants' genotyping data is stored, processed, and securely transferred between Affymetrix and Navigenics' data center. Navigenics' systems are designed to ensure that customer data is kept sufficiently secure and not released to persons not permitted to access the data, either through malicious or inadvertent means. Systems housing customer data are not directly accessible from the internet and the data are not posted on any public web or file transmission protocol (FTP) server. All customer data is stored and transferred in encrypted form.

Potential Risks to Participants

Although the study procedures pose minimal risks to participants, we list the potential risks here:

1. Study assessments: The demographic, medical and family history, and behavioral assessment questionnaires may be time-consuming and/or make some participants uncomfortable. Overall, however, the assessments have been designed to be brief and non-invasive, and are thus unlikely to cause distress.
2. Saliva sample collection: The only known risk related to saliva sampling is the possibility of a dry mouth during collection of the sample. Should this occur, however, it is likely to be experienced for only a brief time and will go away after drinking fluids.
3. Distress associated with genetic risk assessment: A participant's genetic risk information could potentially cause them or their family members some distress, such as by revealing that the participant or their blood relative carries a genetic predisposition for a disease.
4. Accuracy of risk information: Given that the state-of-the-field of GWAS-based disease risk assessment is relatively new, the risk estimates may not be completely accurate, particularly for certain racial/ethnic groups for whom methods for risk assessment are less well-developed. A participant may receive risk estimates that are later revealed to be inaccurate, which could cause distress.
5. Risk of discrimination: In spite of all of the extraordinary measures that will be used, we cannot absolutely guarantee that a participant's identity will never become known. Although genetic information is unique to each participant, individuals do share some genetic information with their children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify the study participant. Similarly, it may be possible that genetic information from the study participant could be used to help identify them. A participant could theoretically be at risk for certain types of discrimination should personal genetic and/or medical data from the study become known.

Potential Risks to Community or Group

1. Ethnic and geographical background: Information on a subject's ethnic and geographical background will be included with other information about them in the database. In future studies, researchers may find that certain genetic variations appear more often in people from certain ethnic groups than in people from other ethnic groups, and that these variations are more common in people with a certain disease. Some individuals may use this information to call attention to these differences in a negative way, or alternatively, others may use the information to downplay differences between ethnic groups and to say that all people's genes are about the same, so the special concerns of different ethnic groups do not need to be respected.

2. ADEQUACY OF PROTECTION AGAINST RISKS

Protection Against Risks to Participants

The safeguards in place to protect participants against potential risks are as follows:

1. Study assessments: To minimize distress stemming from completion of the study assessments, we have designed the assessments to be brief and non-invasive.
2. Saliva sample collection: Participants are encouraged to drink fluids should they experience a dry mouth following saliva collection.

3. Distress associated with genetic risk assessment: Study participants are encouraged to engage in genetic counseling session(s) with a Navigenics certified genetic counselor. Further, to protect against possible distress related to a participant's receipt of genomic risk information that suggests they are at high risk for a particular disease, it is Navigenics' policy is to conduct "proactive outreach" (i.e., they send an email offering genetic counseling services with instructions on how to set up an appointment) to certain individuals/consumers based on their profile of genomic risk results. Their criteria for doing this include any one of the following: (1) homozygous risk for Alzheimer's disease (i.e., two copies of the APOE-ε4 allele); (2) multiple sclerosis estimated lifetime risk of 1.5% or greater; (3) more than two cancers that are color coded orange (see Research Plan or http://www.navigenics.com/demo/tutorial for explanation of color coding); (4) more than eight conditions (overall) that are color coded orange; and (5) any condition for which the individual has a greater than 60% estimated lifetime risk.
4. Accuracy of risk information: Again, to minimize distress resulting from risk estimates that may prove to be unstable over time, participants are given information about this prior to enrolling in the study. Furthermore, leveraging genetic counseling (as described above) can also minimize the possibility of distress related to this issue.
5. Risk of discrimination: To minimize risk of discrimination stemming from breaches of privacy, several precautionary measures are in place. Information from analyses of participants' encrypted samples and their de-identified, encrypted medical information is put into a database at the Scripps Translational Science Institute. This database is in a secure area where only authorized personnel will be allowed to look at this information. The de-identified data is accessible only via a secure server with maximum electronic security measures. Further, it is the case that a recently passed Federal law, Genetic Information Non-discrimination Act (GINA), protects participants from discrimination by employers and health insurance providers.

Protection Against Risks to Community or Group

1. Ethnic and geographical background: Although it is difficult to foresee specific steps that can be taken to minimize the risk that genetic information about certain ethnic groups may be used to call attention to certain groups in a negative way (or that this information may be used to downplay differences between ethnic groups to say that the special concerns of different groups do not need to be respected), we aim to be culturally sensitive in framing research questions and interpretation of all results.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH

There are no direct benefits to the individual subject for participating in the study, although participation does provide each participant with the latest state-of-the field information on his or her DNA (though with their participation, each participant provides payment for this service). The knowledge gained from the study, however, will help researchers better understand the behavioral impact of GWAS-based genetic risk disclosure, and in the long run may inform ways to personalize the delivery of health care to individuals.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

With the proposed work, we aim to characterize consumers of DTC personal genomics services, as well as assess behavioral and psychological response to DTC genetic testing, including potential moderators of response such as level of genetic risk and utilization of genetic counseling services. At this time there is essentially nothing known about the impact of this technology on consumers despite its relatively wide availability and the fact that many individual consumers have already purchased these products. Thus, the proposed work will provide an initial examination of these important questions to which timely answers are critical given efforts currently underway to determine how best to regulate the sale and use of these tests.

5. DATA AND SAFETY MONITORING FOR CLINICAL TRIALS

N/A

INCLUSION OF WOMEN AND MINORITIES

The current proposed work will leverage data collected as part of the Scripps Genomic Health Initiative (SGHI), which is an ongoing longitudinal cohort study of over 4,000 individuals that began in October 2008. Both women and members of minority groups are included in the SGHI, and thus, these individuals will be included in the proposed work, which will involve analysis of SGHI behavioral data. Specifically, in our preliminary data, which consists of 2,779 individuals, women make up approximately 58% of the sample and members of minority groups make up approximately 16% of the sample.

Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: Response to Testing Among Consumers of DTC Personal Genomics Services

Total Planned Enrollment: 5,000

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	210	90	300
Not Hispanic or Latino	2640	2060	4700
Ethnic Category: Total of All Subjects *	2850	2150	5000
Racial Categories			
American Indian/Alaska Native	10	5	15
Asian	215	185	400
Native Hawaiian or Other Pacific Islander	40	10	50
Black or African American	65	70	135
White	2550	1850	4400
Racial Categories: Total of All Subjects *	2880	2120	5000

* The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."

INCLUSION OF CHILDREN

The current proposed work will leverage data collected as part of the Scripps Genomic Health Initiative (SGHI), which is an ongoing longitudinal cohort study of over 4,000 individuals that began in October 2008. One inclusion criterion of the SGHI is that participants must be 18 years of age or older. Therefore, for the proposed work, we will include children age 18 years and older. Since we are requesting funds for analysis of the SGHI data and the SGHI is an existing study with already-specified inclusion/exclusion criteria that exclude children younger than 18 years, we are not able to include children in this age range in our proposed analyses.

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The following letter of support was included as part of the original application and is provided with the permission of Dr. Schork. An additional 7 letters were included in the original application but have been redacted to protect the privacy of individuals providing letters of support.

Scripps

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Dear Cinnamon,

I am writing this to express my unmitigated enthusiasm for our collaborative research proposal that you are spearheading entitled, 'Response to Testing Among Individual Consumers of DTC Personal Genomics Services.' I also want to use this letter as a vehicle for explaining my gratis support of this proposal in the event that reviewers of the proposal have questions about my involvement or commitment to the research.

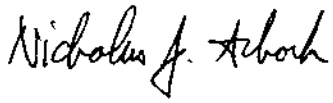
First, as we have discussed, there are many statistical analysis challenges associated with the assessment of change in the context of longitudinal intervention studies. I have been involved in the development of relevant analysis methodologies for some time and feel that our joint discussions and grant proposals are the perfect vehicles for the description, detailed use, and critique of these methodologies. In addition, working with a team of scientists with expertise in different areas – such as yours in psychological assessment, Dr. Madlensky's in genetic counseling, Dr. Topol's in translational science, and my own in statistics and bioinformatics – is really paradigmatic of the type of collaborative research that I feel is imperative if transformative and translational insights are to be obtained from biomedical research.

Second, as you also know, our institute, The Scripps Translational Science Institute (STSI), was awarded a prestigious Clinical and Translational Science Award (CTSA), whose mandate is to foster translational and transformative collaborative research. As the director of the Biostatistics and Bioinformatics components of our Scripps Translational Science Institute (STSI), a large portion of my salary is covered by our CTSA grant. The remainder of my salary is covered by large-scale NIH-funded consortia for which I am responsible for overseeing aspects of the data analysis and the development of analysis methods – many aspects of which have been extended or further

supported by our CTSA award. Thus, I am funded to, in fact, develop data analysis methodologies for researchers in the scientific community at large and to collaborate with others in this capacity.

In terms of consumer response to DTC personal genomics services, this is clearly an area of research that is both controversial and, as such, in need of empirical studies. Our Scripps Genomic Health Initiative cohort provides an opportunity to conduct just such a study, and I am looking forward to working with you on this. If I can be of any further assistance, or if anyone at NIH has any questions about my gratis commitment or position with respect to the proposed research, please do not hesitate to contact me.

Sincerely,



Nicholas J. Schork, Ph.D.

PHS 398 Checklist

OMB Number: 0925-0001
Expiration Date: 9/30/2007

1. Application Type:

From SF 424 (R&R) Cover Page. The responses provided on the R&R cover page are repeated here for your reference, as you answer the questions that are specific to the PHS398.

* Type of Application:

☒ New ☐ Resubmission ☐ Renewal ☐ Continuation ☐ Revision

Federal Identifier: 10353009

2. Change of Investigator / Change of Institution Questions

☐ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:
* First Name:
Middle Name:
* Last Name:
Suffix:

☐ Change of Grantee Institution

* Name of former institution:

3. Inventions and Patents (For renewal applications only)

* Inventions and Patents: Yes ☐ No ☐

If the answer is "Yes" then please answer the following:

* Previously Reported: Yes ☐ No ☐

OMB Number. 0925-0001
Expiration Date: 9/30/2007

4. * Program Income

Is program income anticipated during the periods for which the grant support is requested?

☐ Yes ☒ No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount ($)	*Source(s)

5. Assurances/Certifications (see instructions)

In agreeing to the assurances/certification section 18 on the SF424 (R&R) form, the authorized organizational representative agrees to comply with the policies, assurances and/or certifications listed in the agency's application guide, when applicable. Descriptions of individual assurances/certifications are provided at: http://grants.nih.gov/grants/funding/424

If unable to certify compliance , where applicable, provide an explanation and attach below.

Explanation: Add Attachment