1) **Personalized Genomic Testing for Skin Cancer – Maximizing Utility and Reach – 05/16/17 (v. 10)**
2) **IRB Review History N/A**
3) **Objectives**

This study will have two phases, with an added usability test after Phase I and before Phase 2.
Phase 1: Cognitive Interviews in Spanish.

Phase 2: Personalized Genomic Testing for Skin Cancer (PGT-SC).

The overarching goal of this study is to learn more about how to maximize the availability, comprehension and appropriate uptake of personalized genomics among different populations in New Mexico. The proposed study has been funded as an R01 by NCI for three years.

Aim I: To examine the personal utility (that is, how does personal genomic testing help the individual) of Personal Genomic Testing for Skin Cancer (PGT-SC) in terms of short-term (three months after testing) sun protection, skin screening (i.e., behaviors), communication, melanoma threat and control beliefs (i.e., putative mediators of behavior change). Guided by Protection Motivation Theory (Robberson and Rogers, 1998), **we hypothesize that behaviors and putative mediators will be higher in those who test, compared to those who decline testing or wait-list controls.**

Aim Ia. An important challenge of personal genomics involves the potential for those who receive "negative" genetic feedback to increase risky behaviors (McBride et al., 2010). To examine this potential unintended consequence of testing, we will conduct a subgroup analysis among those who receive average risk PGT-SC findings, examining sun protection at three months as the outcome. Predictors will include baseline skin cancer threat and control beliefs, skin cancer risk factors, and demographics. These findings will be used in future studies to develop messages for groups that receive average risk feedback, which accounts for large segments of those tested for moderate risk susceptibility factors across many diseases.

Aim II: To examine differential reach of PGT-SC across Hispanics and Non-Hispanics, and potential explanations for any differential reach. Reach is defined as the extent to which genomic testing is spread throughout the population. Reach will be measured in individuals as the consideration of the pros and cons of testing and registration of test decision. Additional assessments of reach include baseline survey completion and decision to pursue PGT-SC testing. **We hypothesize that those who are self-identified Hispanic will show reduced reach, but that differences in health literacy, health system distrust, and Hispanic sociocultural factors (Marin G, et al., 1987) including cancer fatalism (Espinosa de Los Monteros and Gallo, 2011), family health orientation (Pasick et al., 2009), and skin cancer misperceptions (Torres et al., 2014; Roman et al., 2013) will explain differences in reach between Hispanics and Non-Hispanics, and provide guidance for future PGT-SC modifications for Hispanics.**

Aim III: Among those who undergo testing, to examine (two weeks after PGT-SC test result receipt) test comprehension, recall, satisfaction, and cancer-related distress, and

whether these outcomes differ by ethnicity (Hispanic versus Non-Hispanic) or health literacy, distrust, sociocultural, or demographic factors. **We hypothesize, based on prior work delivering this intervention in primary care, we will have high test comprehension, accurate feedback interpretation, and low test distress in those who get tested (Kaphingst et al., 2012).**

4) Background

Personalized genomics currently has extremely limited reach (Hindorff et al., 2009; Green and Guyer, 2011). *First,* most gene discovery has not engaged diverse research cohorts (James et al., 2008). *Second,* the few translational research efforts that address "real world" genomic challenges and opportunities have engaged those with higher socioeconomic status and health literacy (Khoury et al., 2011). *Third,* ethnic and racial minorities are less likely to participate in basic genomics research, and are also less likely to utilize available genomic technologies, even when they are offered (Pagan et al., 2009; Bloss et al., 2010; Suther et al., 2009). Ideally, we should all have fair access to the knowledge gained from sequencing the human genome, but if these trends continue, we will know little about how to maximize availability, comprehension, and appropriate uptake of personalized genomics across large subpopulations that stand to benefit from it.

To begin to address this, The Multiplex Study led by the National Human Genome Research Institute (NHGRI) used population-based recruitment strategies in Detroit, Michigan to evaluate an Internet-provided offer of genomic testing for common diseases, including melanoma, the most serious form of skin cancer. Study findings indicate that this approach is *feasible* – resulting in high test comprehension, accurate feedback interpretation, and low test distress in those who sought testing (Kaphing et al., 2012). Yet this study did not include Hispanics nor assess behavioral outcomes.

Personalized genomic testing for skin cancer (PGT-SC) is an ideal context to extend Multiplex to a new population, and new outcomes. Skin cancers are preventable, curable, very common in the general population (Lazovich et al., 2012), and disproportionately increasing in Hispanics (Rouhani et al., 2010). The NHGRI Multiplex Study offered testing for melanoma risk via the melanocortin 1 receptor gene (*MC1R*) (Wade et al., 2010) because *MC1R* is common in the general population (50% ≥1 high risk variant) (Demenais et al., 2010), interacts with sun exposure (Udayakumar andTsao, 2009), and confers risk (2-3 fold (Raimondi et al., 2008); consistent with most moderate risk variants), *even in those with darker skin types*. *MC1R* feedback is a promising vehicle to raise risk awareness and protective behavior in the general population, including Hispanics who are largely unaware of their melanoma risks (Friedman et al., 2994; Hu et al., 2009; Piptone et al., 2002; Robinson et al., 2011). We will conduct a randomized controlled trial examining internet presentation of the risks and benefits of PGT-SC (shown to be feasible in Multiplex) versus wait-list controls who are not offered testing, comparing personal utility and reach in a general population, English or Spanish-speaking cohort in Albuquerque, New Mexico, where there is year-round sun exposure.

Prior investigator collaborations. This transdisciplinary effort will bring together the combined expertise of investigators – many of whom have productive, longstanding collaborations already - to integrate up-to-date research findings from their respective disciplines, a necessary step given that the rapid unfolding of new cancer genomic, communication, and behavioral science findings is the expected reality of these fields (Wade et al., 2009). We employ a Multiple PI Plan. Dr. Jennifer Hay, Principal Investigator is an expert in risk communication and behavior change who has worked with Dr. Marianne Berwick, Principal Investigator, a genetic epidemiologist and a leader in the field of the genetic factors in melanoma for over 10 years. Drs. Hay and Berwick conducted studies examining family communication and health behavior change (screening, sun protection) in melanoma families, and found a high rate of discussion about melanoma risk in melanoma families, (Hay et al., 2005) that different patterns of family communication after melanoma diagnosis influence adoption of prevention strategies, (Hay et al., 2005; Hay et al., 2008) inconsistent adoption of such strategies in survivors, (Majumdar et

al., 2009) and that behavioral outcomes associated with hypothetical melanoma genetic testing differ based on positive versus negative risk feedback. (Hay et al., 2012).

University of New Mexico (UNM) primary care patients are receptive to skin cancer genomic communication; UNM Hispanics report higher skin cancer misconceptions. Drs. Hay and Berwick conducted a pilot study in the UNM 1209 Clinic to examine 1) patients' receptivity to behavioral research studies in skin cancer and genetics, 2) to document levels of sunscreen and protective clothing use, shade-seeking, and health provider skin cancer screening examinations, 3) to examine prior health information-seeking and family cancer discussions, and 4) prevalence of accurate skin cancer beliefs. Most (71%) participants were female and they ranged in age from 19-81 years (n=50), with racial/ethnic subgroups consistent with the Albuquerque population (46% were Hispanic, 35% were Non-Hispanic White, 6% Native American, 3% African American, and 10% other). Nine percent had not completed high school, and 55% had household incomes less than $30k/year. About one third (30%) reported a family skin cancer history and 7% a personal skin cancer history. About two-thirds (66%) reported interest in behavioral skin cancer research, and while few (17%) had heard of genetic testing marketed directly to consumers, two thirds (76%) said they would be interested in learning more about genetic testing for skin cancer. Sun protection and skin cancer screening levels were consistent with recent national data; 29% reported that they consistently used sunscreen, 62% wore a shirt with sleeves, 34% a hat, and 47% sought shade often or always while outside on a sunny day. Even fewer (26%) had ever received a health provider skin examination. Non-Hispanic Whites reported more consistent use of sunscreen, and were more likely to have received a prior health provider skin examination than Hispanics and other racial/ethnic groups (all p values <0.01). Two-thirds (62%) reported that they were moderately or highly likely to develop skin cancer. Predominant reasons for heightened risk included current or past sun exposure, fair skin, and family history or genetic factors. Spontaneous health information-seeking was common, with 72% reporting that they had ever sought information on medical topics, predominantly via the internet. Over half (62%) had sought cancer information. About half (55%) had talked about cancer risk, and 37% about skin cancer risk, in their family. Those with higher perceived skin cancer risk talked more about it with their family (r=0.34, p=0.001) and were more interested in skin cancer behavioral research participation (r=0.26, p=0.01). We assess skin cancer misconceptions as an explanation for reduced PGT-SC reach in Aim II of the current study, because Hispanics reported more skin cancer misconceptions than Non-Hispanic Whites in our UNM pilot study. Over half of Hispanics endorsed confusion about which skin cancer recommendations to follow, and significant proportions of Hispanics agreed with the statement "it seems likely almost everything causes skin cancer" (24%); and "people with skin cancer would have pain or other symptoms prior to diagnosis" (24%;Torres et al., 2014). Also in our prior work with nationally representative samples, we found that Non-Hispanic Whites had higher awareness of accurate skin cancer causes, prevention strategies, and symptoms than Hispanics. Hispanics reported higher levels of information overload and misconceptions. (Hay et al., 2009).

References

Bloss CS, Ornowski L, Silver E, et al. Consumer perceptions of direct-to-consumer personalized genomic risk assessments. *Genetics in medicine : official journal of the American College of Medical Genetics.* Sep 2010;12(9):556-566.

Demenais F, Mohamdi H, Chaudru V, et al. Association of MC1R variants and host phenotypes with melanoma risk in CDKN2A mutation carriers: a GenoMEL study. *Journal of the National Cancer Institute.* Oct 20 2010;102(20):1568-1583.

Friedman LC, Bruce S, Weinberg AD, Cooper HP, Yen AH, Hill M. Early detection of skin cancer: racial/ethnic differences in behaviors and attitudes. *Journal of cancer education : the official journal of the American Association for Cancer Education.* Summer 1994;9(2):105-110.

Green ED, Guyer MS. Charting a course for genomic medicine from base pairs to bedside. *Nature.* Feb 10 2011;470(7333):204-213.

Hay JL, Ostroff JS, Martin A, et al. Skin cancer risk discussions in melanoma-affected families. *Journal of cancer education : the official journal of the American Association for Cancer Education.* Winter 2005;20(4):240-246.

Hay J, Shuk E, Brady M, Berwick M, Ostroff J, Halpern A. Family communication after melanoma diagnosis. *Archives of dermatology.* 2008;144(4):553-554.

Hay J, Shuk E, Zapolska J, et al. Family communication patterns after melanoma diagnosis. *Journal of Family Communication.* 2009;9(4):209-232.

Hay J, Coups EJ, Ford J, Dibonaventura M. Exposure to mass media health information, skin cancer beliefs, and sun protection behaviors in a United States probability sample. *Journal of the American Academy of Dermatology.* Jul 9 2009.

Hay JL, Baguer C, Li Y, Orlow I, Berwick M. Interpretation of melanoma risk feedback in first-degree relatives of melanoma patients. *Journal of cancer epidemiology.* 2012;2012:374842.

Hay J, Kaphingst KA, Baser R, Li Y, Hensley-Alford S, McBride CM. Skin cancer concerns and genetic risk information-seeking in primary care. *Public health genomics.* 2012;15(2):57-72.

Hindorff LA, Sethupathy P, Junkins HA, et al. Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. *Proceedings of the National Academy of Sciences of the United States of America.* Jun 9 2009;106(23):9362-9367.

Hu S, Parmet Y, Allen G, et al. Disparity in melanoma: a trend analysis of melanoma incidence and stage at diagnosis among whites, Hispanics, and blacks in Florida. *Arch Dermatol.* Dec 2009;145(12):1369-1374.

James RD, Yu JH, Henrikson NB, Bowen DJ, Fullerton SM. Strategies and stakeholders: minority recruitment in cancer genetics research. *Community genetics.* 2008;11(4):241-249.

Kaphingst KA, McBride CM, Wade C, et al. Patients' understanding of and responses to multiplex genetic susceptibility test results. *Genetics in medicine : official journal of the American College of Medical Genetics.* Jul 2012;14(7):681-687.

Khoury MJ, Clauser SB, Freedman AN, et al. Population sciences, translational research, and the opportunities and challenges for genomics to reduce the burden of cancer in the 21st century. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology.* Oct 2011;20(10):2105-2114.

Lazovich D, Choi K, Vogel RI. Time to get serious about skin cancer prevention. *Cancer Epidemiol Biomarkers Prev.* Nov 2012;21(11):1893-1901.

Mujumdar UJ, Hay JL, Monroe-Hinds YC, et al. Sun protection and skin self-examination in melanoma survivors. *Psycho-oncology.* Jan 13 2009.

Pagan JA, Su D, Li L, Armstrong K, Asch DA. Racial and ethnic disparities in awareness of genetic testing for cancer risk. *Am J Prev Med.* Dec 2009;37(6):524-530.

Pipitone M, Robinson JK, Camara C, Chittineni B, Fisher SG. Skin cancer awareness in suburban employees: a Hispanic perspective. *Journal of the American Academy of Dermatology.* Jul 2002;47(1):118-123.

Raimondi S, Sera F, Gandini S, et al. MC1R variants, melanoma and red hair color phenotype: A meta-analysis. *International Journal of Cancer.* 2008;122(12):2753-2760.

Robinson JK, Joshi KM, Ortiz S, Kundu RV. Melanoma knowledge, perception, and awareness in ethnic minorities in Chicago: recommendations regarding education. *Psycho-oncology.* Mar 2011;20(3):313-320.

Rouhani P, Pinheiro PS, Sherman R, et al. Increasing rates of melanoma among nonwhites in Florida compared with the United States. *Arch Dermatol.* Jul 2010;146(7):741-746.

Suther S, Kiros GE. Barriers to the use of genetic testing: a study of racial and ethnic disparities. *Genetics in medicine : official journal of the American College of Medical Genetics.* Sep 2009;11(9):655-662.

Torres S, Ramos M, Leverence R, Bowen D, Berwick M, Hay J. Skin Cancer Risk Reduction Behaviors, Cancer Communication, and Skin Cancer Beliefs in Hispanics in a Southwestern Primary Care Practice. *Californian Journal of Health Promotion.* See Appendix III for the In Press Manuscript.

Udayakumar D, Tsao H. Moderate- to low-risk variant alleles of cutaneous malignancies and nevi: lessons from genome-wide association studies. *Genome Med.* 2009;1(10):95.

Wade CH, McBride CM, Kardia SL, Brody LC. Considerations for Designing a Prototype Genetic Test for Use in Translational Research. *Public health genomics.* Sep 3 2009.

Wade CH, McBride CM, Kardia SL, Brody LC. Considerations for designing a prototype genetic test for use in translational research. *Public health genomics.* 2010;13(3):155-165.

5) Inclusion and Exclusion Criteria

This study will have two phases, plus a usability phase after the Cognitive Interviews and before Phase II.

Phase 1: Cognitive Interviews in Spanish.

Phase II: Personalized Genomic Testing for Skin Cancer (PGT-SC).

In Phase I, patients will be eligible for the study if they have been registered in 1209 Clinic for at least two years and assigned a primary care physician, aged >18 , and are fluent in Spanish. We will exclude adults that are unable to consent, individuals who are not yet adults (infants, children, teenagers) and prisoners. Pregnant women will be eligible to participate.

Usability Phase. We will collect input from up to 10 patients from the 1209 Clinic concerning website usability (overall look and feel and website functioning) to allow for any further website refinement prior to website launch. Patients will be eligible for this study if they have been registered in 1209 Clinic for at least two years and assigned a primary care physician, speak English or Spanish and are over the age of 18. We will exclude adults that are unable to consent, individuals who are not yet adults (infants, children, teenagers) and prisoners. Pregnant women will be eligible to participate.

In Phase II, patients will be eligible for the study if they have been registered at a UNM Clinic for six months and assigned a primary care provider, aged >18, and are fluent in either English or Spanish. We will exclude adults that are unable to consent, individuals who are not yet adults (infants, children, teenagers) and prisoners. Pregnant women will be eligible to participate. All participants in Phase II will be consented and interviewed at 1209 University Clinic, OSIS Orthopedic Clinic at 1213 University Boulevard, NE, the Family Medicine Clinic, the Center for Employee and Occupational Health Services, both at 2400 Tucker, NE or the North Valley Clinic. Individuals who usually attend another UNM Clinic (Atrisco Heritage Center for Family and Community Health, Northeast Heights Clinic, North Valley Clinic, Westside Clinic, Southeast Heights Center for Family and Community Health, Family Medical Center, Lobo Care Clinic, Senior Health Center, or Southwest Mesa Center for Family and Community Health) and are accompanying a patient from these Clinics will be eligible for Phase II.

6) Number of Subjects (Recruitment Target)

Phase 1: We anticipate that we will conduct cognitive interviews of **40** subjects fluent in Spanish, 20 men and 20 women, who either completed high school or did not complete high school (see phase I recruitment table).

Phase I Recruitment Table	Gender	
Education	Male	Female
Completed high school/equivalent or greater	10	10
Did not complete high school or equivalent	10	10

Usability Phase: We will conduct the usability survey in **up to 10** subjects who attend the 1209 Clinic.

Phase II: We anticipate that we will conduct a baseline assessment of **650** subjects (see SOMBRA Study Flow, p. 6). They will then be randomized to a "Wait List Control Group of **120** subjects and a PGT-SC group of **530** subjects. All **530** subjects will be offered MC1R genetic testing. The "Wait List Control Group (**120** subjects) will be offered the MC1R test after the **Three Month Follow Up Questionnaire**. Accordingly, all **650** subjects will be offered MC1R testing. Of those offered, based on our prior experience, we anticipate 30-50 percent will accept an invitation for testing.

Phase II: Recruitment Tables	**Ethnicity**	
	Hispanic	**NHW**
Waitlist Controls – n = 120	60	60
PGT-SC Group – n=530	265	265

7) **Recruitment Methods**

Phase I: Project Assistants (PAs) will approach primary care patients in the UNM 1209 clinic with a **Clinic Flyer and Phase I FAQ** for Clinic Patients explaining the main purpose of the study as well as eligibility requirements and the **NCI Skin Cancer Pamphlet in English or Spanish** (Spanish version; "Anyone can get skin cancer," *https://pubs.cancer.gov/ncipl/detail.aspx?prodid=P237*). They will explain the study and review the **Information Sheet** document for Phase I. If the potential participant decides to participate, they will evaluate all materials (Clinic Flyer, FAQ for Clinic Patients, NCI Skin Cancer Pamphlet, Phase II Consent, Screening Survey, Refuser Survey, Baseline Questionnaire, Introduction Letters - Groups 1 and 2, Sombra Gift Card Form, Sombra Appointment Card, Sombra Website, Donor Mailing Instructions, Specimen Collection Instructions, Sombra Results A (for average risk feedback), Sombra Results B (for increased risk feedback), Two Week Risk Feedback Comprehension Questionnaire, and Three Month Follow Up Questionnaire) in a semi-private area of the Clinic.

Usability Phase: To conduct usability of the website, we will recruit up to 10 patients from our target population (1209 Clinic). 1209 clinic waiting room patients will be approached and invited to participate in the project usability testing of the website. The PA will explain the purpose of the SOMBRA website and of usability testing, and interested participants will be given an Information Sheet and usability testing will be conducted. Participants will be asked to use the website in the presence of a project assistant (PA), thinking out loud as they use it. The PA will observe participants and take notes on the problems identified in using the website, and then ask a brief set of questions about the website (See Usability Questions). The interaction will take approximately 45 minutes or less. The PA will summarize the results of the usability evaluation for each participant, and these results will be used for website improvement. Participants will receive a $20 Target gift card for their valued time and effort.

Phase II: Clinic Flyers and NCI Skin Cancer Pamphlets in both English and Spanish will be available at various spots throughout the Clinic. All Staff will know about the study and be available to answer questions and help direct potential participants to the bilingual PAs. The PAs will approach primary care patients or a person accompanying them who attends another UNM Clinic (see above) in the UNM 1209 clinic, the OSIS Orthopedic Clinic, the Family Medicine Clinic, the Center for Employee or North Valley Clinic and Occupational Health Services with a Clinic Flyer and Phase II FAQ for Clinic Patients explaining the main purpose of the study as well as eligibility requirements and the NCI Skin Cancer Pamphlets (available in English and Spanish versions; "Anyone can get skin cancer," *https://pubs.cancer.gov/ncipl/detail.aspx?prodid=P237*). They will explain the study and review the Informed Consent -2 and **UNMHSC_HIPAA_Authorization** documents. If the potential participant decides to enroll, they will then be given a Screening Survey and, if they decide not to enroll, a very

short Refuser Survey. If they decide to continue the PA will conduct a Baseline Questionnaire in a semi-private area of the Clinic.

8) **Study Timeline**

This study will take place in three phases:

Phase 1: Cognitive Interviews in Spanish.

Usability Phase: Testing usability of the website.

Phase II: Personalized Genomic Testing for Skin Cancer (PGT-SC).

Phase I Cognitive Interviews: Spanish Translation and PGT-SC Website launch (4-6 months). First, the MSKCC Linguistic and Cultural Competence Team (Mr. Javier Gonzalez and Dr. Francesca Gany, Co-Investigators) within the Immigrant Health and Cancer Disparities Service at MSKCC will provide Spanish translations of all English **IRB approved** study materials with the assistance of Erika Robers at UNM (Clinic Flyer, FAQ for Clinic Patients, (NCI Skin Cancer Pamphlet was translated by NCI), Consent – Number 2, Screening Survey, Refuser Survey, Baseline Questionnaire, Introduction Letter for Groups 1 and 2, Sombra Gift Card Form, Sombra Appointment Card, Sombra Website, Donor Mailing Instructions, Specimen Collection Instructions, Sombra Results A (for average risk feedback), Sombra Results B (for increased risk feedback), Two-Week Risk Feedback Comprehension Questionnaire, and Three Month Follow Up Questionnaire).

An amendment will be submitted to the IRB following cognitive interview assessments and results for approval of the Spanish translations prior to the use of these translated materials in Phase II. Our bilingual PAs will approach Spanish speaking primary care patients in 1209 clinic with the Clinic Flyer, the Phase I FAQ for Clinic Patients and NCI Skin Cancer Information Pamphlet in Spanish ("Anyone can get skin cancer," https://pubs.cancer.gov/ncipl/detail.aspx?prodid=P237) and will conduct a series of up to 60 minute cognitive interviews with Phase 1 consented eligible participants to ensure the comprehensibility and acceptability of the translations in our Albuquerque population with 40 Spanish-speakers with balanced stratification across gender and education level (> high school; < high school). Co-Investigator Dr. Keith Hunley, a genetic anthropologist with expertise in the cultural and genetic background of New Mexico Hispanics, will work with Ms. Maria Otero (PA) to construct a series of questions to be included in the cognitive interviews to address Hispanic sociocultural issues relevant to skin cancer genetic testing; such questions will include: What comes to mind when you hear the term "skin cancer"? What comes to mind when you hear the term "genetic testing"? Would you want to have genetic testing for skin cancer? Why or why not? What would be your language preference if you were receiving genetic testing results? Who would you trust to give you information about genetic testing? These open-ended responses will be summarized and tabulated. Ms. Otero and the team will discuss the interpretation of the responses. Based on these findings, we will modify the information given to patients and in the surveys.

There will be web-based computer modules, providing genetic, skin cancer and MC1R educational materials and the testing invitation (Baseline Questionnaire) developed by Dr. David Buller at Klein Buendel, Inc. (KB), in Colorado. Dr Buller specializes in the development of health education programs and multimedia products in the areas of chronic disease prevention and control. The modules are: 1) What genetic testing can and cannot tell you, 2) Skin cancer and genes, 3) Your rights if you take part in genetic research, and 4) Your decision to be tested or not .The website contains four modules to include

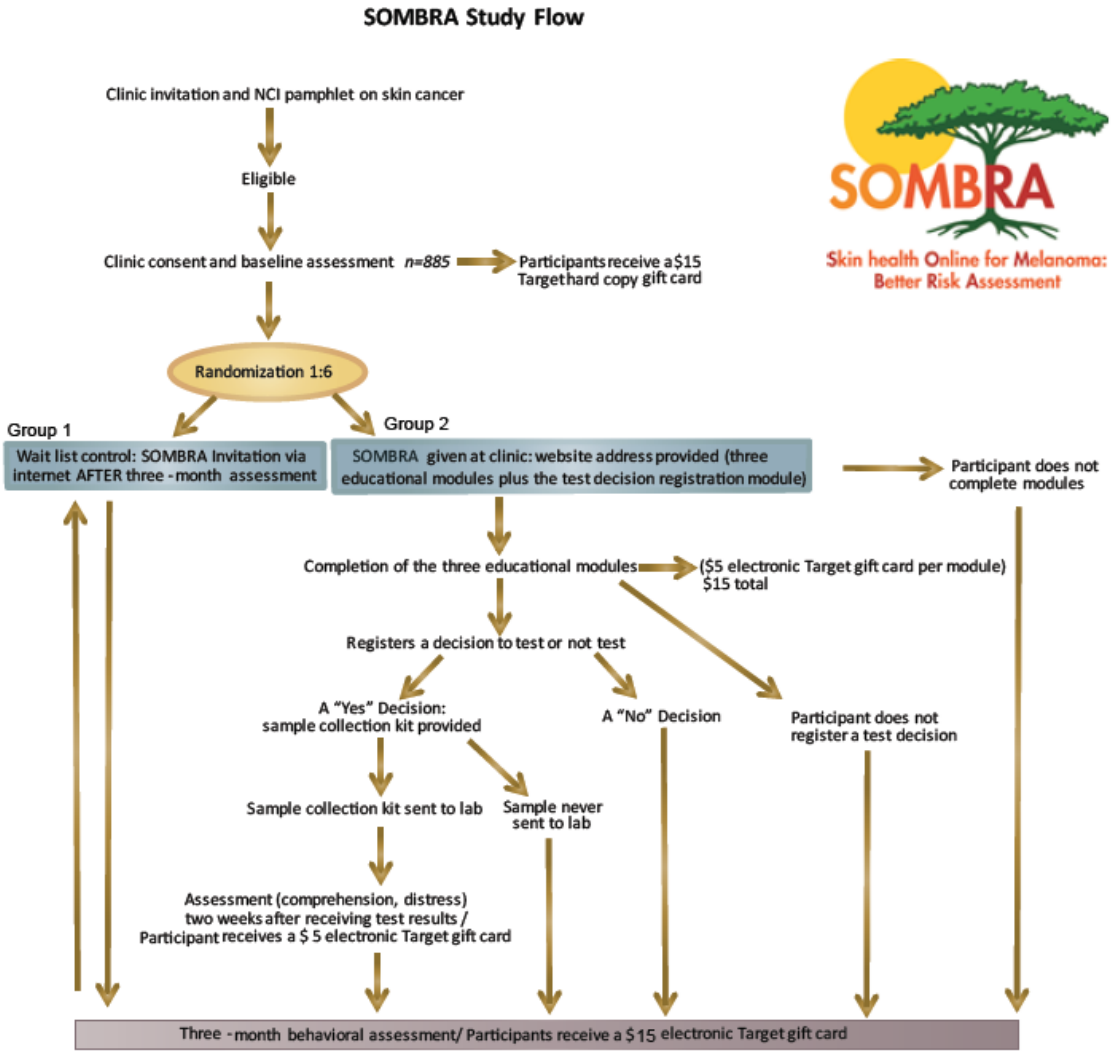
comprehension questions "wrapped" inside a website interface. The interface will include help files, navigation devices, and data collection code. It will be tested in-house for code stability, and beta tested prior to exportation to the Web server at Klein Buendel. MSKCC and Klein Buendel will not have any access to PHI and will only receive de-identified data.

Usability Phase.

After website development, we will collect input from up to 10 patients from 1209 Clinic concerning website usability (overall look and feel and website functioning) to allow for any further website refinement prior to website launch.

Phase II Personalized Genomic Testing for Skin Cancer (PGT-SC, 20 months).

A) Clinic physician-provider study preparation. Prior to beginning the **PGT-SC**, study Dr. Jessica Bigney, Clinic Director and Co-Investigator, will conduct an in-service meeting with 1209 Clinic physicians and staff to introduce the study, discuss current state-of-the-science in skin cancer genomics, and provide them with brief written information. Dr. Berwick will do the same for the Orthopedic Clinic the Family Medicine Clinic ,the Center for Employee and Occupational Health Services and the North Valley Clinic. This will allow physicians to respond to patient inquiries, as well as requests for skin cancer screening and genetic counseling. Detailed questions will be referred to Drs. Berwick and Hay. Dr. Bigney, Ms. Lena Celestine, Dr. Jennifer K. Philips, Dr. Denece Kesler or Dr. Val xxxx will provide additional updates with physicians on request throughout the study.



B) Recruitment (See Figure Above, Study Flow). Our bilingual PAs will approach primary care patients or someone accompanying them who attends another UNM Clinic (see above) in 1209 Clinic, the Orthopedic Clinic, the Family Medicine Clinic, the Center for Employee and Occupational Health Services or the North Valley Clinic with the Clinic Flyer the Phase II FAQ for Clinic Patients, and the NCI Skin Cancer Information pamphlet (available in English and Spanish versions; "*Anyone can get skin cancer*," https://pubs.cancer.gov/ncipl/detail.aspx?prodid=P237). They will determine if potential subjects are interested in participation.

C) Baseline Assessment. All participants approached will be asked to complete a three minute Eligibility Screening and a Screening Survey to determine their interest in and eligibility for study participation, as well as basic demographics. If they are eligible and interested in study participation, the PA will fully explain the study and the participant will provide written informed consent (Consent - Number 2 and UNMHSC_HIPAA_Authorization), receiving a copy of the signed consent form. The PA will guide them to complete the Baseline Questionnaire in the clinic in a semi-private space with dedicated study computer (tablet or laptop computer).

Based on prior research, we anticipate that 30% of those approached will participate and complete the Baseline Questionnaire. Sample size estimates indicate that a total number of participants of 885 is necessary to evaluate our outcomes.

After completion of the Baseline Questionnaire facilitated by the PA, participants will receive a $15 Target Gift card for their time and effort. They will sign a Sombra Gift Card Form and receive a Sombra Appointment Card. They will then be randomized to Group 1 - wait-list controls or to Group 2 to consider PGT-SC through a secure website (randomized and balanced across Hispanic and Non-Hispanic ethnicity, n=120 in control arm, n=530 in PGT-SC arm). "Hispanic" ethnicity will be recorded by self-report. Patients will choose Spanish or English study materials.

D) PGT-SC Invitation. (**Group 2** – n=530)

Participants randomized to the PGT-SC study arm will view materials on the SOMBRA Website via Internet from a home, work, library or community-based organization computer, or alternatively through a paper version of the modules if they prefer. Internet reach in Albuquerque is >80% and WiFi is available throughout the city. All participants will be asked to consider the four educational modules regarding PGT-SC. The PGT-SC modules are:

1) What genetic testing can and cannot tell you,

2) Skin cancer and genes,

3) Your rights if you take part in genetic research, and

4) Your decision to be tested or not.

After each module, participants will be asked to answer a series of questions regarding knowledge and satisfaction with the content of each module, and after section 4 they will be asked to register a decision as to whether they wish to have a skin cancer genetic test, or not. Participants will only be able to register a test decision if they have already read and completed the questions on the first three educational modules. Knowledge and satisfaction questions are part of each module. Those who complete these steps will receive an additional $5 target Gift card incentive for each module for a maximum a total of $15 in Target Gift card incentives. There is no incentive associated with the 4th module on the decision to conduct genetic testing or not.

Registration of a test decision (yes; no) is our primary assessment of "reach" in this study. We expect a minimum of 30% of participants who complete the Baseline Survey to register a genetic test decision, and that this will reach 50% in some subgroups, including those with higher literacy. Additional assessments of "reach" include completion of the baseline survey and decision to pursue PGT-SC testing (yes; no).

Those who register a decision to proceed with testing will receive a DNA buccal cell test kit with instructions (Donor Mailing Form and Specimen Collection Form), which will allow them to provide a saliva sample for genetic testing, pre-paid postage envelope, and instructions in English and Spanish for buccal cell collection. Based on The Multiplex Study, we anticipate that up to 50% of participants who consider PGT-SC will return a saliva sample for genetic testing. The Molecular Epidemiology Laboratory at UNM HSC will conduct testing; participants will receive PGT-SC results by mail (or by email, if they prefer) within one month.

We will employ state-of-the-art methods of risk communication used with high comprehension in the Multiplex Study, guided by Co-Investigator Dr. Kimberly Kaphingst, who originally developed Multiplex Study risk communication materials. These materials combine verbal and pictorial displays of risk information and denominator information. We will also provide written information to clarify risk level given that individuals tend to rely on the gist of the information provided (See SOMBRA Result A for average risk individuals and SOMBRA Result B for higher risk individuals)

<u>All</u> subjects who participate in PGT-SC genetic testing will receive a telephone call two weeks after results are mailed, to assess PGT-SC result comprehension and potential distress (see Two Week Risk Feedback Comprehension Assessment) and to answer any questions they may have. All those who

complete this Assessment will receive a $5 Target Gift card as thanks for their effort. Based on prior literature documenting low levels of distress in those undergoing genetic testing for high-risk mutations, and among those found to carry *CDKN2A* mutations, we anticipate low levels of distress regarding PGT-SC feedback. Anyone who reports high distress will be referred to Clinic Director and Co-Investigator Dr. Jessica Bigney, who addresses distress issues regularly in the UNM clinic. If they wish, a genetic counselor will be available.

E) Three-month follow-up.

All participants who completed Baseline Assessments (whether tested or not) will be contacted for assessment by telephone three months after PGT-SC testing (Three Month Follow Up Questionnaire). Participants who complete this three-month follow up assessment will receive a $15 Target Gift card for their valued study participation.

F) Group 1 genetic testing option.

Those 120 participants randomized to the control group will receive an offer for PGT-SC directly after the three-month follow-up assessments. They will be offered testing, and of those who pursue testing, will receive results by mail or by email, sent by the PA who enrolled them, and a two-week follow-up telephone call to assess result comprehension and potential distress.

G) Summary.

We anticipate that patients will be enrolled over an approximately 12 month period, complete assessments and receive feedback within 20 months. Thus individuals are estimated to be in the study for 3 months and the enrollment and assessment period overall will last as long as 20 months total. Primary analyses will be completed in the 6 months following the 24 months period of participation; the entire study will take 3 years.

9) **Study Endpoints.**

Primary endpoints are based on the 3-month follow up questionnaires. The primary study endpoints include personal utility of Personal Genomic Testing for Skin Cancer (PGT-SC) in terms of short-term (three months after testing) sun protection, skin screening (i.e., behaviors), communication, melanoma threat and control beliefs (i.e., putative mediators of behavior change), as well as differential reach of PGT-SC across Hispanics and non-Hispanics, as well as potential explanations for any differential reach. These will include the construct/measures listed below:

Construct/Measure	Prior work/psychometrics	Assess point
Sun protection and skin screening (Sunscreen, shade seeking, clothing and hat usage) on separate 5-point scales (never-always); health provider screening (no/yes).	Item reliability ≥80%. (Ganz, 2008)	B, 3-month
Family/physician communication. Frequency, content of communication with physicians, family, and friends regarding skin cancer risk, interest in genetic information; 4-point scales (not at all-a lot).	Items used with high comprehensibility in population-based studies (Hay 2005, 2009, 2012, 2014)	B, 3-month, (interest in genetic information only)

Perceived skin cancer threat belief (Witte 1996). Includes assessment of risk perceptions (verbal, percent likelihood, comparison) on separate scales (5 to 10-point) from low-high, with "don't know" option (Waters 2013); worry, assessed with 4-point items (never-all the time. Perceived skin cancer control beliefs (Witte 1996) Includes skin cancer prevention self-efficacy (7 items, on separate 4-point scales; not at all-extremely capable), skin cancer prevention response-efficacy (7 items, on separate 4-point scales; not at all to extremely important).	Widely used perceived risk items drawn from prior health behavior research (Weinstein 1982), Lerman's cancer worry scale (Lerman 1991), and perceived cancer severity (Aiken 1994). Control belief items (Bandura 1986) predicting uptake of cancer prevention behaviors; adapted for skin cancer prevention (Hay 2006).	B, 3-month (risk perception question only)
Hispanic ethnicity	For initial sampling frame (50%) Hispanic, self-report as per Baseline survey.	B
Health Literacy includes 3 items: level of confidence in filling out medical forms independently, frequency of needed assistance reading hospital materials, and frequency of problems learning about medical conditions because of difficulty reading hospital materials (5-point scales, none of the time-all the time).	Single Item Literacy Screener Items (Chew 2004, 2008) are feasible in primary care populations, with more limited respondent burden compared to TOFHLA or REALM; Area under Receiver Operating Characteristic Curve analyses indicate good sensitivity for diverse literacy levels.	B
Health System Distrust includes 9 items assessing two domains; values and competence distrust in 5-point scales (strongly agree-strongly disagree).	The Health System Distrust Scale (Shea 2008) **i**s validated in primary care against established physician trust scales; reliability overall (0.83), Values (0.73); Competence (0.77).	B
Sociocultural factors includes a 15-item assessment of Cancer Fatalism on 2-point scales (agree/disagree), a 4-item assessment of Family Health Orientation: social influences on learning more about health, social influences on doing more about health, how motivated they are to do what important others want them to do, how much their health choices affect others (7-point scales, strongly disagree- strongly agree), and 10-item assessing Skin Cancer Misconceptions, including	Cancer Fatalism predicts cancer prevention activities (Espinosa de Los Monteros, 2011); we use Powe Cancer Fatalism Scale (Powe 1995) examining fear, pessimism, death inevitability, and predetermination beliefs. It is well validated (Espinosa de Los Monteros, 2011), and reliable (.88). Family Health Orientation assessed via social influences on health information seeking and behavior change from Multiplex (Hay 2012), and	B

preventability, treatability, and information overload about skin cancer (Agree/Disagree).	Skin Cancer Misconceptions items from the Health Information National Trends Survey 2007 (NCI, 2007) and found to be lower among Hispanics (Torres 2014).	
Knowledge and satisfaction with PGT-SC invitation modules, all on 7-point scales (strongly disagree-strongly agree; see Appendix I for items).	Adopted from the NHGRI Multiplex Study (Kaphingst 2010).	Embedded in PGT-SC invitation (Appendix I)
Test result comprehension includes recall, perceived clarity, interpretation and recall, believability, and test regret on closed, open-ended scales.	Adopted from the NHGRI Multiplex Study (Kaphingst 2012, McBride 2009).	Risk feedback comp. assessment
Cancer-related Distress is assessed through 7 items on separate 5-point scales (not at all-extremely).	Impact of Events Scale – Revised Intrusive thoughts subscale (Horowitz 1979) is widely used with good internal and test–retest reliability; good ability to distinguish those with cancer distress (Joseph 2000; Thewes 2001).	Risk feedback comp. assessment; 3-month
Demographics (birth year, US nativity, survey language choice, gender, education, income, race/ethnicity); Internet availability.	Standard demographic questions; Internet availability (Nelson 2004).	B
Melanoma risk factors (personal and family melanoma history; phenotype, sunburn hx).	Heavily used items from prior epidemiology research (Gandini 2005).	B

References for Endpoints:

Aiken LS, West SG, Woodward CK, Reno RR, Reynolds KD. Increasing screening mammography in asymptomatic women: evaluation of a second-generation, theory-based program. *Health Psychol.* Nov 1994;13(6):526-538.

Bandura A. *Social foundations of thought and action: a social cognitive theory.* Englewood Cliffs, NJ: Prentice-Hall; 1986.

Chew LD, Griffin JM, Partin MR, et al. Validation of screening questions for limited health literacy in a large VA outpatient population. *Journal of general internal medicine.* May 2008;23(5):561-566.

Chew LD, Bradley KA, Boyko EJ. Brief questions to identify patients with inadequate health literacy. *Family medicine.* Sep 2004;36(8):588-594.

Espinosa de Los Monteros K, Gallo LC. The relevance of fatalism in the study of Latinas' cancer screening behavior: a systematic review of the literature. *International journal of behavioral medicine.* Dec 2011;18(4):310-318.

Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: I common and atypical naevi. *European journal of cancer (Oxford, England : 1990).* 2005;41(1):28-44.

Glanz K, Yaroch AL, Dancel M, et al. Measures of sun exposure and sun protection practices for behavioral and epidemiologic research. *Archives of Dermatology.* Feb 2008;144(2):217-222.

Hay JL, Ostroff JS, Martin A, et al. Skin cancer risk discussions in melanoma-affected families. *Journal of cancer education : the official journal of the American Association for Cancer Education.* Winter 2005;20(4):240-246.

Hay JL, Oliveria SA, Dusza SW, Phelan DL, Ostroff JS, Halpern AC. Psychosocial mediators of a nurse intervention to increase skin self-examination in patients at high risk for melanoma. *Cancer Epidemiol Biomarkers Prev.* Jun 2006;15(6):1212-1216.

Hay J, Coups EJ, Ford J, Dibonaventura M. Exposure to mass media health information, skin cancer beliefs, and sun protection behaviors in a United States probability sample. *Journal of the American Academy of Dermatology.* Jul 9 2009.

Hay J, Kaphingst KA, Baser R, Li Y, Hensley-Alford S, McBride CM. Skin cancer concerns and genetic risk information-seeking in primary care. *Public health genomics.* 2012;15(2):57-72.

Hay JL, Baser R, Weinstein ND, Li Y, Primavera L, Kemeny MM. Examining intuitive risk perceptions for cancer in diverse populations. Health Risk Soc 2014;16:227-242.

Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: a measure of subjective stress. *Psychosom Med.* May 1979;41(3):209-218.

Joseph S. Psychometric evaluation of Horowitz's Impact of Event Scale: a review. *Journal of traumatic stress.* Jan 2000;13(1):101-113.

Kaphingst KA, McBride CM, Wade C, Alford SH, Brody LC, Baxevanis AD. Consumers' use of web-based information and their decisions about multiplex genetic susceptibility testing. *Journal of medical Internet research.* 2010;12(3):e41.

Lerman C, Trock B, Rimer BK, Jepson C, Brody D, Boyce A. Psychological side effects of breast cancer screening. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association.* 1991;10(4):259-267.

McBride CM, Alford SH, Reid RJ, Larson EB, Baxevanis AD, Brody LC. Characteristics of users of online personalized genomic risk assessments: implications for physician-patient interactions. *Genetics in medicine : official journal of the American College of Medical Genetics.* Aug 2009;11(8):582-587.

National Cancer Institute. Health Information National Trends Survey. 2007; http://hints.cancer.gov. Accessed Accessed Oct 1, 2013.

Nelson DE, Kreps GL, Hesse BW, et al. The Health Information National Trends Survey (HINTS): development, design, and dissemination. *Journal of health communication.* Sep-Oct 2004;9(5):443-460; discussion 481-444.

Powe BD. Cancer fatalism among elderly Caucasians and African Americans. *Oncology nursing forum.* Oct 1995;22(9):1355-1359.

Shea JA, Micco E, Dean LT, McMurphy S, Schwartz JS, Armstrong K. Development of a revised Health Care System Distrust scale. *Journal of general internal medicine.* Jun 2008;23(6):727-732.

Thewes B, Meiser B, Hickie IB. Psychometric properties of the Impact of Event Scale amongst women at increased risk for hereditary breast cancer. *Psycho-oncology.* Nov-Dec 2001;10(6):459-468.

Torres S, Ramos M, Leverence R, Bowen D, Berwick M, Hay J. A Pilot Study of Skin Cancer Risk Reduction Behaviors, Cancer Communication, and Skin Cancer Beliefs in Hispanics in a Southwestern Primary Care Practice. *Californian Journal of Health Promotion.*2014.(12):95-100.

Weinstein ND. Unrealistic optimism about susceptibility to health problems. *Journal of behavioral medicine.* Dec 1982;5(4):441-460.

10) Research Setting

This study will be carried out at the UNM 1209 Primary Care Practice site, the Orthopedic Clinic at OSIS, the Family Medicine Clinic, the Center for Employee and Occupational Health Services and through the Internet. All participants in Phase II will be consented and interviewed at 1209 University Clinic, The Orthopedic Clinic at OSIS, the Family Medicine Clinic or the Center for Employee and Occupational Health Services. Individuals who usually attend another UNM Clinic (Atrisco Heritage Center for Family and Community Health, Northeast Heights Clinic, North Valley Clinic, Westside Clinic, Southeast Heights Center for Family and Community Health, Family Medical Center, Lobo Care Clinic, Senior Health Center, or Southwest Mesa Center for Family and Community Health) and are accompanying a patient from one of the Clinics will be eligible for Phase II.

The UNM Cancer Center Molecular Epidemiology Laboratory in will carry out MC1R testing. In case of lack of access to this laboratory space, MC1R testing would be conducted at the UNM Human Tissue Repository (HTR), or UNM CTSC, or by the company Genewiz. In the event of activation of this backup plan, any samples sent would be de-identified.

Development of the website will be carried out by Dr. David Buller at Klein Buendel in Denver, Colorado.

Translation of intervention materials, consent form, study flyers and surveys will conducted by MSKCC Linguistic and Cultural Competence Team with assistance from Ms. Erika Robers at UNM.

Cognitive interviews to ensure high comprehensibility and acceptability of the translations will be conducted by Ms. Maria Otero and Ms. Erika Robers.

The Department of Psychiatry & Behavioral Sciences at MSKCC will conduct data analysis on de-identified data.

11) Study Methods

*The timeline above gives very detailed information about study methods.
Subjects will be approached at their Clinic and asked if they are interested in participating. Individuals accompanying Clinic patients and who attend another UNM Clinic are eligible to participate.

They will then discuss the study with the bilingual interviewer and, if they are eligible agree and sign informed consent. All baseline surveys will then be completed with the PA in the clinic.

Identifiers will be collected and remain at UNM for mailing and follow-up. Subjects will then be de-identified at the end of the study (after 3 years).

Subjects will receive compensation for participation. ALL consented subjects will receive a $15 Target Gift card after completion of the Baseline Questionnaire; those in the randomized to the wait list control Group 1 will receive compensation for the baseline survey and the three-month survey. Those randomized to Group 2, the PGT-SC arm will then be given information modules through the internet (or on paper if they prefer). They will be asked if they would like to participate in genetic testing for MC1R. Those randomized to receive PGT-SC who complete the online educational modules will be compensated $5 Target Gift card per educational module, with a maximum of $15 possible. Additionally, among those who elect genetic testing, we will assess distress levels two weeks after the PGT -SC genetic results have been received, and will compensate participants for their time with a $5 target Gift card. All participants who completed Baseline Assessments (whether tested or not) will be contacted for the final assessment by telephone approximately three months after recruitment. Participants who complete the three-month outcome assessment will receive a $15 Target Gift card. This level of compensation is reasonable for the level of effort required for subjects.

12) Data and Specimen Banking

For participants who indicate that they want to participate in genetic testing, we will mail saliva collection kits. They will give a sample of saliva and mail these back to the study in pre-addressed, stamped envelopes. These will be delivered to the UNM Molecular Epidemiology Laboratory at UNM HSC. DNA will be extracted and sequenced for MC1R only, a gene that is important for pigmentation. Specimens will be destroyed when a good test result is obtained. Data will be kept until the end of the study when it will be destroyed. Kirsten White, the Manager of the Molecular Epidemiology Laboratory, will be the only person with access to the specimens. Each specimen will have a separate ID number that links it to the donor. When the specimen has been assayed, the de-identified information will then be given to the study team (J. Hay, M. Berwick, data analyst) and to the donor.

No information, other than participant study number, will be stored with the specimen. Results will be identifiable to authorized personal at UNM (PAs, Kirsten White and Dr. Marianne Berwick) until the end of the study. Genetic testing will be done for MC1R only by sending the DNA from the participants to an outside accredited laboratory but will be completely de-identified.

SOMBRA Protocol for DNA Extraction

Important Points before starting:

- Perform all centrifugation steps at room temp (15-25◦C)
- Preheat the water bath at 56◦C.
- If Buffer AL or Buffer ATL contains precipitates, dissolve by heating to 70◦C with gentle agitation.
- Make sure Buffer AW1 and Buffer AW2 are prepared (follow specified instructions) before purification steps are initiated.

Day 1:

1. Add 500 ul of 100% ethanol to each sample and mix by inversion (or vortexing) for one minute. The tissue will now appear chalky white.
2. Centrifuge the samples at 12,000 rpm for 5 minutes at room temperature and remove the supernatant.
3. Repeat step 1 and 2 once for a total of two ethanol washes.
4. Dry the tissue pellet by inversion under the hood until the ethanol is evaporated. This may take anywhere from 25-60 minutes depending on pellet size. At this point the pellet can be frozen at -80C or proceed with the next step.
5. To the pellet, add 120 µl of Buffer ATL, and 20 µl Proteinase K (QIAGEN; 20 µg/µl stock). Mix thoroughly by pulse-vortexing for 15 sec. (note: begin this step in the morning)
6. Place the 1.5 ml tube in a water bath and incubate at 56◦C. Pulse vortex for 15 seconds every hour. Incubate samples at 56◦C overnight.

Day 2:

1. Add 60 µl of Buffer ATL, and 10 µl Proteinase K to the sample in the morning and continue to incubate at 56◦C. Pulse vortex for 15 seconds every hour and then continue incubation overnight.

Day 3:

Before starting:

- Warm AE Buffer to 37°C.
- Chill 100% ethanol on ice.
- Make labels for 2mL collection tubes and non-siliconized 1.5mL microfuge tube for each sample.

1. Add 200 µl Buffer AL, close the lid and mix by pulse-vortexing for 15 s. If a precipitate forms, incubate samples at 56◦C for 10 min. Following this step allow the samples to cool to RT (~10 min). Do not place these samples on ice, or the precipitate will form again. While the samples are cooling, place 100% on ice to prepare for the next step.
2. Add 200 µl ice-cooled ethanol (100%), close the lid and mix by pulse-vortexing for 15 sec.

Incubate at room temperature for 5 min.

3. Pulse centrifuge the 1.5 ml tube to remove drops from the inside of the lid.
4. Carefully transfer the entire lysate from step 3 to the QIAamp MinElute column without wetting the rim. Centrifuge at 6000 x g (8000 rpm) for 1 min. (If the lysate has not completely passed through the membrane after centrifugation, centrifuge again until the column is empty.)
5. Place the MinElute column in a clean 2 ml collection tube and discard the collection

tube containing the flow through.

6. Carefully add 500 µl Buffer AW1. Centrifuge 6000 x g (8000 rpm) for 1 min.
7. Place the MinElute column in a clean 2 ml collection tube and discard the collection tube containing the flow through.
8. Carefully add 500 µl Buffer AW2. Centrifuge 6000 x g (8000 rpm) for 1 min. (note: be careful when removing the tubes from the rotor, do not allow the flow through to contact the column during this step)
9. Place the MinElute column in a clean 2 ml collection tube and discard the collection tube containing the flow through.
10. Centrifuge at 20,800 x g (14,000 rpm) for 3 min to dry the membrane completely.
11. Place the MinElute column in a clean 1.5 ml microcentrifuge tube and discard the collection tube containing the flow-through.
12. Apply (to the center of the column; on the membrane) 20 µl AE Buffer (warmed to 37°C). Close the lid and incubate at room temperature for 5 min.
13. Centrifuge 20,800 x g (14,000 rpm) for 1 min.
14. Repeat elution step (Step 12 and 13 above). Optional: repeat steps 12 and 13 multiple times.

SOMBRA Sequencing Protocol

Genotyping. MC1R will be sequenced using a 1125bp PCR-amplified fragment to cover the coding region. Information on primers and cycling parameters is listed in supplemental data.

Excess nucleotides and primers will be removed using shrimp alkaline phosphatase/exonuclease I using standard conditions.

The BigDye® terminator cycle sequencing followed under standard conditions using one of four primers to address the carboxy – terminus - , transmembrane - , and the amino – terminus regions. Products were sequenced on an ABI Prism 3700 (Applied Biosystems, Foster City, CA) and electropherograms will be read by an independent reviewer using the Sequencher software v.4.05 (Gene Codes Corporation, Ann Arbor, MI).

13) Data Management

Information Collected. We will identify each subject with a unique ID linked to PHI (name, address, telephone number, age, sex and ethnicity) which is only kept by the study team at UNM and overseen by Dr. Berwick. These files will be stored in space belonging to Dr. Berwick and maintained in a locked cabinet in a locked room in a secure building. This link will be destroyed at the end of the study, upon completion of data analysis. **Only UNM study personnel will have access to this PHI.** Dr. Berwick has the responsibility for the transmission and receipt of any data.

Overall data processing and missing data imputation. We will first examine aspects of data quality and distributional assumptions to ensure statistical integrity and accuracy: 1) data skewness, kurtosis, and parametric assumptions; 2) intention-to-treat (ITT) principles; 3) missing data considerations; and 4) control of potentially inflated Type-I errors due to multiple statistical tests. First, data skewness and kurtosis will be examined to determine whether each variable significantly deviates from normality. If so, we will employ data transformations by taking a log or square root of the skewed variables, or by using the Box-Cox transformation or kernel estimation techniques (Diggle et al., 2002) to determine the best-fitting parametric density. Second, we assume that up to 20% of the respondents will be unreachable at our three-month follow-up assessment; missing assessments may be amenable to imputation by several powerful techniques that can handle both continuous and categorical data (Graham et al., 2997; Schafer and Olsen, 1998). A related approach is the use of Hierarchical Linear Models (HLM) (Raudenbush and Bryk, 2002) to use all available behavioral outcomes data since HLM does not carry out list-wise deletion by default, thus the statistical power loss due to missing data may be minimal. We will apply the intention-to-treat (ITT) principle (Nich and Carroll, 1997). An ITT analysis in Aim I (Nich and Carroll, 1997; Willett et al., 1998) would assume missing data is related to lack of sun protection adherence. We may use the Pattern-Mixture Model to examine whether or not missed follow-up assessments are associated with baseline characteristics with safeguards to minimize

model overfit (Hedeker and Gibbons, 1997). Finally, to control for potentially inflated type-I error rate due to multiple comparisons, analyses can also incorporate a multiple comparisons method, such as a False Discovery Rate-controlling procedure, which is more powerful than simple Bonferroni corrections.

References for Data Processing

Diggle P, Heagerty P, Liang KY, Zeger SL. *Analysis of Longitudinal Data.* Oxford, Great Britain: Oxford University Press; 2002.

Graham JW, Hofer SM, Donaldson SI, MacKinnon DP, Schafer JL. Analysis with missing data in prevention research. In: Bryant K, Windle M, West S, eds. *The science of prevention: methodological advances from alcohol and substance abuse research*. Washington, D.C.: American Psychological Association; 1997:pp. 325-366.

Hedeker D, Gibbons RD. Application of random-effects pattern-mixture models for missing data in longitudinal studies. *Psychological Methods.* 1997;2:64-78.

Nich C, Carroll KM. Now you see it, now you don't: a practical demonstration of random regression versus traditional ANOVA models in the analysis of longitudinal follow-up data from a clinical trial. *Journal of Consulting and Clinical Psychology.* 1997;65:252-261.

Raudenbush SW, Bryk AS. *Hierarchical Linear Models.* Vol 1. 2 ed. Newbury Park, CA: Sage Publications, Inc.; 2002.

Schafer JL, Olsen MK. Multiple imputation for multivariate missing data problems: a data analyst's perspective. *Multivariate Behavioral Research.* 1998;33:545-571.

Willett JB, Singer JD, Martin NC. The design and alalysis of longitudinal studies of development and psychopathology in context: statistical models and methodological recommendations. *Dev Psychopathol.* Spring 1998;10(2):395-426.

Data encryption and safeguards. Data will be collected and encrypted via a web application through a secure connection. All database and application servers will be hosted at MSKCC where only de-identified data are stored. Data collection over the Internet will include only de-identified information as per HIPAA requirements (NIH, 2004) and no identifiers will be collected over the Internet (http://cphs.berkeley.edu/hipaa/hipaa18.html). Additional data encryption and safeguard procedures are planned, including Secure Socket Layer (SSL) encryption of the online data entry forms at an enterprise security level comparable to that used in online commerce. Data will be stored with encrypted databases on servers protected behind the MSKCC institutional firewall to guard against cyber attacks such as password guessing or port snooping. Software patches are automatically updated daily to ensure the latest security fixes.

14) **Provisions to Monitor the Data to Ensure the Safety of Subjects**

N/A

15) **Withdrawal of Subjects**

Subjects are free to withdraw from the study at any time. This will not affect them or their health care.

16) **Risks to Subjects**

This is a minimal risk study; there are no physical risks posed by this study. However, it is possible that receiving information about one's risk for skin cancer could cause psychological distress. We will monitor subjects closely who receive that information. In the Randomized Clinical Trial, there is potential risk of loss of privacy given that the Baseline Assessment might be conducted in the clinic waiting room.

We will give the genetic results by mail (or email, if requested); the PA who enrolled the participant will mail or email that information. If the participant has concerns, then an appointment with a Dr. Bigney will be made, so that he/she can discuss these further.
As research has the possibility of breach of confidentiality, all possible efforts are made to limit that risk.

17) **Potential Benefits to Subjects**

Potential benefits include learning more about skin cancer prevention and skin cancer risk awareness. Although we cannot guarantee that participants may benefit directly from study participation, prior study participants have reported that they enjoyed providing researchers with greater knowledge of their experience in hopes of facilitating the design of cancer prevention materials and in possibly benefiting others. Given the potential gains to participants, the ratio of risk to benefits is quite low and reasonable.

18) **Vulnerable Populations**

N/A

19) **Multi-Site Research**

Dr. Marianne Berwick of the University of New Mexico and Dr. Jennifer Hay at Memorial Sloan-Kettering are Multiple-Principal Investigators. Dr. Berwick is supervising the data collection in New Mexico and Dr. Hay is supervising the data analyses in New York. We plan to use the UNM HRRC as the central IRB of record. Both sites have had input into the development of the protocol, consent documents and HIPAA Authorization. All required approvals will have been obtained at both UNM HRRC and MSKCC. Any modifications will be communicated to each site, including approval by the site's IRB of record. As noted elsewhere in the protocol, all engaged participating sites will safeguard data as required by local information security policies. Any non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

The proposed research is a low-risk behavioral trial. Research staff will carefully monitor each participant's emotional reaction during study interviews, and offer referral when appropriate.

All serious AEs (e.g., medical occurrences resulting in death) that occur during the study defined by the given protocol, regardless of the relation to the research, must be reported to the IRB by telephone, email or FAX within 24 hours of the investigator's awareness of

the occurrence of the event. The PI's will report serious AEs to the UNM IRB and will disseminate information to other agencies as necessary. These initial reports are followed by a safety report which is a written account of a serious AE determined by a sponsor/investigator to be both related to the treatment under investigation and unexpected in nature. Serious AE's will be summarized annually in the IRB application for continuation or termination of research.

As per MSKCC and the University of New Mexico IRB policies, the PI is required to notify the IRB promptly of any unanticipated problems involving risks to study participants or others that occur. The PIs will monitor the progress of the trial and safety of the participants on an ongoing basis. The procedures of this study, such as regular meetings with research staff, will ensure discussion and reporting of all possible outcomes including adverse events. If the adverse event is due to the study and is unexpected, the PIs (Hay and Berwick) will draft a safety report and send a copy to MSKCC and UNM IRBs. The IRB committees will serve as an objective review mechanism. This policy-procedure means that any potential conflict of interest inherent in the PIs being the sole reviewers of serious adverse events is avoided. The PI's at each site will meet with staff at least weekly and hold a teleconference at least weekly. If an adverse event occurs in-between teleconference (or in person meetings), then an urgent teleconference will be held to communicate the adverse event.

Interim results will not be available.

The study would only be closed under unusual circumstances. At that time, the PI's will notify both IRBs.

20) **Community-Based Participatory Research/Field Research**

N/A

21) **Sharing of Results with Subjects/Incidental Findings**

We will share results of genetic testing with individual study participants (SOMBRA Result A – average risk results, and SOMBRA Result B – increased risk results). The results are **not actionable, but informational**. The PA will mail results to the study participant as was done in the Multiplex Study, or if the participant wishes – by email. If there are any signs of distress in any way, we will work with Dr. Jessica Bigney, the Director of the Clinic, and with Shawnia Ryan, a cancer genetic counselor at the UNM Cancer Center, as necessary. Additionally, we will be assessing distress levels two weeks after the PGT-SC results have been received, and at all follow-up time points. Through the ongoing monitoring process of the study (e.g., regular meetings with research staff), the PIs and Co-Investigators will be informed of any concerns/distress that occur among study participants.

22) **Resources Available**

Qualifications of Investigators: Dr. Marianne Berwick has been conducting epidemiologic research internationally and locally for the past 27 years. Her CV is attached. Dr. Jennifer Hay has been conducting psychological and behavioral research for more than 15 years. Her CV is attached.

Project Assistants will interview individuals who agree. They are bi-lingual in English and Spanish, with either a Bachelor's degree and at least two years' experience that is applicable to the duties listed in the job description, or a Master's degree with at least six

months' experience that can be demonstrated to be applicable to the duties listed in the job description.

Recruitment plan/access to potential recruits. Dr. Jessica Bigney, Director of the 1209 UNM Primary Care Clinic, is a co-investigator and will assist the study with logistics at the Clinic and in working with the Clinic staff. Previously, we conducted a pilot study of 100 patients at the clinic with positive results and no negative feedback.

We will post a flyer (Clinic Flyer) explaining the study to the population of individuals attending the Clinic. In the pilot study, we recruited 100 patients in 3 days; therefore, our plan to spend several months to recruit 885 patients seems quite feasible. We will meet with the staff at the clinic to explain our goals. There are quiet spots within the clinic where we can easily discuss the study with interested individuals, explain Informed Consent and HIPAA and conduct the Baseline Questionnaire.

Resources that subjects might require during their participation in this research include contact information for the PAs as well as Dr. Berwick. In addition, a member of the IRB is named as a person to contact with any human subject concerns the participant might have. These will be given in the Consent form that the subject signs and retains a copy of as well as in information (Introduction Letter – Group 1 and Introduction Letter – Group 2) explaining the study that the participant will take with him.

23) **Prior Approvals/Attachments Requiring Signatures**

Prior approvals include HRRC approval at UNM and IRB approval at MSKCC. Dr. Kimberly Page, the Division Chief for Epidemiology, Biostatistics and Preventive Medicine, has reviewed and approved the Department Review as she has been authorized by Dr. Moseley, the Department of Internal Medicine Chair to do so.

Confidentiality

Participant data will be stored in a manner that protects against unauthorized disclosure of personally identifiable data. All MSKCC and UNM research project personnel are required to be trained in human subject protection. All data at UNM will be stored in space belonging to Dr. Berwick and maintained in a locked file cabinet in a locked office, in a locked building. Procedures will be used to require proper authentication to access data files in print and digital database formats. All collected research data will be maintained at MSKCC on a secure file server to which only designated people will have access. Personally identifiable data will be stored in a separate database from the remainder of project details with unique participant identifiers used to map the data sets as needed.

We keep all records in coded format, in locked file cabinets, in a locked room. Only people associated with this project, such as Dr. Berwick at University of New Mexico and other necessary trained staff at Memorial Sloan Kettering, University of New Mexico, the Food and Drug Administration, or other sponsors, such as the National Cancer Institute, would be able to see individual data. Participants' research records are confidential. Your name or any other personal identifying information will not be used in reports or publication resulting from this study. All information is presented in group form, and no one would be able to tell if any individual person is in these groups.

Identifiable data will be stored in password protected files at UNM HSC in space belonging to Dr. Berwick and maintained in the office as noted above. For all participants, personally identifiable data will be collected from participants by authorized research project personnel.

Information on name, phone number, and mailing address will be essential for sending genomic testing kits and for giving information by telephone. Age, sex and ethnicity are necessary to determine study eligibility and for data analysis. These PHI are also essential for follow up. Names and addresses are additionally essential in order for us to send participants their financial incentives for completing assessments.

For both Phase I cognitive interview participants and Phase II PGT-SC participants, data will be used exclusively for research purposes. Confidentiality of each subject's self-report information, as well as genetic data, will be protected with the utmost care. Self-report information and genetic information will be housed in de-identified computer data files. A "cross-over" file matching ID number with participant identifying information (name, address and phone number) will be maintained and stored separately from the data in a password-protected database at UNM HSC on a secure server. The link between participant identification numbers and data will be kept in a locked file cabinet in a locked office within a secured building. Only study personnel will have access to the crossover file.

24) Provisions to Protect the Privacy of Subjects

During the recruitment, consent and data collection, subjects will be able to sit in a private or semi-private section of the Clinic out of earshot of non-study team members. The research team will be collecting PHI and transferring that to Dr. Berwick. HIPAA authorization will be obtained.

25) Compensation for Research-Related Injury

It is difficult to imagine that any research-related injury would occur. However, the consent form will clearly state that the patient will be responsible for covering this, although the study team will assist the participant in obtaining any necessary care.

26) Economic Burden to Subjects

- There will not be any cost to the participant for any study procedure, visit or drug/devices.
- Treatment for adverse events will be paid by the participant, as stated in the consent form.

27) Consent Process

Consent

The consenting process was explained in Sections 5-8:

Phase I: Our bilingual PAs will approach Spanish speaking primary care patients in 1209 clinic with the Clinic Flyer, the Phase I FAQ for Clinic Patients and the NCI Skin Cancer Pamphlets (Spanish version; "Anyone can get skin cancer," https://pubs.cancer.gov/ncipl/detail.aspx?prodid=P237). They will explain the study and review the Information Sheet in Spanish and will then conduct a series of 30-45 minute cognitive interviews to ensure the comprehensibility and acceptability of the translations in our Albuquerque population with 40 Spanish-speakers with balanced stratification across gender and education level (> high school; < high school).

For Phase I only we are requesting a Waiver of Documentation of Consent. The information sheet given to patients to explain the study is attached.

This research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. We are also requesting a waiver of HIPAA Authorization for all subjects in Phase I. We are not obtaining any protected health information from participants.

Usability Phase: Our bilingual PAs will approach English or Spanish speaking primary care patients in 1209 clinic with the Clinic Flyer and the NCI Skin Cancer Pamphlets (Spanish version; "Anyone can get skin cancer," https://pubs.cancer.gov/ncipl/detail.aspx?prodid=P237). They will explain the study and review the Information Sheet in English or Spanish and will then the usability evaluation of the website with up to 10 participants.

For this phase we are requesting a Waiver of Documentation of Consent. The Information Sheet given to patients to explain the usability survey is attached in English and in Spanish.

This research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. We are also requesting a waiver of HIPAA Authorization for all subjects in the Usability Phase. We are not obtaining any protected health information from participants.

Phase II: Our bilingual PAs will approach primary care patients in the UNM 1209 Clinic, the Orthopedic Clinic at OSIS, the Family Medicine Clinic. the Center for Employee and Occupational Health Services or the North Valley Clinic with NCI Skin Cancer Pamphlets (available in English and Spanish versions; "Anyone can get skin cancer," https://pubs.cancer.gov/ncipl/detail.aspx?prodid=P237). They will explain the study and review the informed consent and HIPAA documents in English or in Spanish. If the potential participant decides to enroll, they will then be given a Screening Survey, sign the Consent form and HIPAA (and receive a copy for themselves) and a Baseline Questionnaire in a private area of the Clinic.

The potential participant will have as much time as he or she wishes to decide to participate. At each subsequent contact, once an individual has been consented, the PA will make sure that the participant wishes to continue by asking such questions as "Do you have any new questions or concerns?"

28) **Drugs or Devices**

N/A