Using MC1R Genotype to Impact Melanoma Risk Behavior

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BACKGROUND

Prevention and early detection can reduce the burden of morbidity and mortality due to melanoma. Melanoma is the fifth most common cancer in the US; over 76,100 persons will develop melanoma in 2014 (Howlader et al. 2014). Overall melanoma incidence rates continue to rise particularly among men and older persons (Howlader et al. 2014). The majority (84%) of persons are diagnosed with localized disease for which 5-year survival is ~98%. For these individuals, primary preventive behaviors like sun protection, use of protective clothing or sunscreen, and avoidance of artificial sources of ultraviolet light could potentially reduce melanoma risk. The remainder of persons will be diagnosed with regional (AJCC stage III) or distant (AJCC stage IV) melanoma that carries a poor 5-year survival rate: 62% and 16%, respectively (Howlader et al. 2014). For the 12,000+ persons diagnosed with non-localized disease each year, early detection (secondary prevention) could result in identification of low risk localized primary lesions for which complete surgical removal of lesions is largely curative.

Melanoma occurs in individuals without traditional phenotypic risk characteristics. Despite the stereotype that melanoma strikes only persons with fair complexions, for example persons with red hair color or who do not readily tan, a large number of melanomas arise in individuals with 'darker' phenotypic traits. Using population-based cancer registries, the Genes, Environment, and Melanoma (GEM) study enrolled over 2400 persons with first primary melanoma from across nine international sites. Among participants, 32% reported having brown hair, 20% reported having dark eyes, 43% responded having low propensity to burn, 59% reported good propensity to tan, and 87% reported mild or no freckling (Berwick et al. 2006). In a case-control study of over 950 melanoma patients, 65% reported having dark hair, 37% reported having dark eyes, 61% responded having low propensity to burn, 76% reported a propensity to tan, and 58% reported some or no freckling (Kanetsky et al. 2010).

***MC1R* genotype conveys information about melanoma risk in persons who do not exhibit traditional melanoma phenotypic risk characteristics.** The melanocortin-1 receptor, *MC1R*, gene encodes a protein central to pathways that signal the production of melanins. *MC1R* exhibits impressive genetic variability, with the majority of individuals carrying at least one variant. Inheritance of specific *MC1R* high-risk variants is a robust marker for increased risk of melanoma, consistently seen across varied populations of European descent. We validated these findings among 779 incident melanoma subjects and 325 controls, but also demonstrated that the association between *MC1R* high-risk variants and melanoma was stronger in or limited to individuals with protective phenotypes such as those who tanned well after repeated sun exposure (OR=2.4; 95% CI 1.6-3.6), had dark hair (OR=2.4; 95% CI 1.5-3.6), or had dark eyes (OR=3.2, 95% CI 1.8-5.9) compared to those who did not tan after repeated sun exposure (OR=0.60; 95% CI 0.06-5.9), had red or blond hair (OR=0.86, 95% CI 0.14-5.4 and OR=0.99, 95% CI 0.41, 2.4, respectively) and had blue/grey or green/hazel eye color (OR=1.8, 95% CI 1.0-3.2 and OR=1.3, 95% CI 0.64-2.7, respectively) (Kanetsky et al. 2010). We noted this same pattern of increased melanoma risk associated with high-risk *MC1R* genotypes among persons who did not freckle and who tanned after exposure to first strong summer sun. These results were supported by meta-analysis of published data (Kanetsky et al. 2010). Further support comes from the M-SKIP study, which pooled data from over 5000 melanoma cases and 12,000 controls (Pasquali et al. 2014). Thus, *MC1R* genotype provides melanoma risk information in individuals who would not be identified as high risk based on their phenotypes or exposures alone and who are unaware of their constitutional risk imparted by inherited genetics.

Public health impact of screening for *MC1R* risk genotypes may be large. There is potential for substantial public health impact when using *MC1R* genetic information in conjunction with phenotype and/or exposure data. The etiologic fraction (EF) denotes the proportion of patients that develop melanoma as a result of inheritance of *MC1R* variants. We determined the EF of the high-risk *MC1R* variants ranges from 33% among dark haired individuals to 42% among dark eyed individuals (Kanetsky et al. 2010). After applying these estimates to the proportion of melanoma that occurs in individuals within these phenotype groups from the population-based GEM study, results suggest that 8 to 33% of all melanomas could be attributable at the population level to inheritance of high-risk *MC1R* variants. These calculations imply that knowledge of *MC1R* genotype may be an important mechanism for targeting melanoma education and screening to persons with protective 'darker' phenotypes. If effective, melanomas may be prevented or detected early when surgical cure is highly likely.

Sun seeking behaviors. Melanoma most likely results from several factors, but increases in sun exposure and associated sunburn, especially at young ages, bear a particularly strong association with subsequent melanoma development (Armstrong et al. 1993, Gandini et al. 2005, Chang et al. 2009). Sun avoidance during periods of peak UV radiation and the adoption of protective measures when exposed are factors that theoretically could reduce melanoma risk. Exposure to intermittent, intense sunlight has been suggested as the most important preventable risk factor (Armstrong et al. 1993). Studies have indicated that modification of sun protection behaviors can lead to positive outcomes, including a reduced number of melanocytic nevi (moles), which are strong melanoma risk markers (English et al. 2006). Unfortunately, less than half of the U.S. population engages in any form of sun protection (Hall et al. 1997). Further, most people do not seek shade while outdoors on sunny days, and the minority wears sun protective clothing (Coups et al. 2008).

Skin examinations. Most often, melanoma is a highly visible cancer that facilitates early identification and detection increasing the likelihood of successful cure (Koh et al. 1992). Early melanoma can be identified by physicians or patients using guidelines for examining new and/or changing lesions. Skin self-examinations are important, and the identification of melanocytic lesions by patients or other family members is a common way by which a majority (Brady et al. 2000) of skin cancer is detected (Koh et al. 1992, Weinstock et al. 1999). While a skin examination by a physician is more likely to detect thinner lesions compared to skin self-examination by non-physicians (Terushkin et al. 2009), studies have noted that those performing skin self-examinations are diagnosed with thinner melanomas compared to those not performing this self-assessment (Berwick et al. 1996, Carli et al. 2003, McPherson et al. 2006). Increasing patient skin awareness and knowledge of melanoma signs and symptoms through educational means could improve the ability of non-physicians to detect earlier lesions (Oliveria et al. 1999).

Although skin self-examination prevalence is low in the general population, greater uptake of skin self-examination may be linked to access of various forms of information. In 2005, the age-adjusted prevalence of total-body skin examination among adults in the U.S. was 16% (Lakhani et al. 2011). An earlier, large survey of primary health care visitors (n=2126) reported that 9 to 18% had completed a thorough skin self-examination (Weinstock et al. 2004). A subgroup (n=668) of participants was randomly selected to receive an intervention aimed at increasing skin self-examination rates. The intervention included instructions to perform skin self-examinations, video, brief counseling and follow-up reminders. The 668 patients in the comparison group received a diet

intervention. After 12 months, the skin-examination intervention group showed a 19.3% difference in skin self-examination rate (95% CI, 13.0-25.7%) compared to controls (Weinstock et al. 2007).

Skin cancer in Hispanic/Latinos (H/L). Although lifetime risk of melanoma among H/L is lower (approximately 1 in 190 individuals) than among white non-Hispanics, overall survival is poorer because more are diagnosed with regional or late stage disease. Among the 73% of H/L diagnosed at early-stage localized disease, for which 5-year survival approaches 98%, sun avoidance, use of protective clothing or sunscreen, and elimination of artificial sources of ultraviolet light (i.e., primary prevention) could have potentially reduced melanoma risk (Hu et al. 2009; Jaimes et al. 2013; Rouhani et al. 2010). For the remaining 27% of H/L who are diagnosed with regional or distant disease, both of which carry poor 5-year survival rates of 62% and 15% respectively (Howlader et al. 2015), early detection (i.e. secondary prevention) could result in identification of low-risk localized primary lesions for which complete surgical removal of lesions is largely curative.

In contrast to the small overall number of melanoma cases in H/L, over 6000 new cases of keratinocyte cancers (i.e., squamous cell carcinoma (SCC) and basal cell carcinoma (BCC)) were diagnosed in Puerto Rico in 2005, representing about 300% increase in incidence since 1974 (De La Torre-Lugo et al. 2010). Rates of keratinocyte cancers in H/L living in Florida are challenging to determine because diagnoses of these cancers are not routinely captured by state or national cancer registries. A population-based study conducted in New Hampshire-a largely non-H/L, low UV exposure state-noted an approximate 10% and 4.5% annual increase in incidence of SCC and BCC, respectively, between the years of 1979-1980 and 1993-1994 (Karagas et al. 1999). Although keratinocyte cancers, in particular BCC, impart low risk of death, they are commonly diagnosed and carry a hefty disease burden on health care expenditures (Housman et al. 1999). Among H/L, skin cancer *primary prevention* has potential to reduce risk of these more common skin cancers, and *secondary prevention* could result in simplified surgical procedures resulting from the detection of smaller lesions (Hoorens et al. 2016).

***MC1R* variants in Hispanic populations living in the Tampa Bay area.** Melanoma incidence is trending upward among Hispanics living in the United States and Puerto Rico (Gonzalez-Fernandez and Sanchez, 1999; Hu et al. 2009). Of particular concern is the poorer overall survival from melanoma among Hispanics due to diagnoses at late stage disease (Hu et al. 2009; Rouhani et al. 2010; Jaimes et al. 2013). However, information on the prevalence and distribution of *MC1R* variants in Hispanic individuals is limited. Knowledge of the spectrum and distribution of the *MC1R* genotypes among Hispanic individuals will lay the foundation for future investigations of whether *MC1R* variants are robust markers of melanoma risk in this population, and by extension whether interventions based on inheritance of high-risk *MC1R* genotype-with the goal of increasing melanoma prevention behaviors-may be generalizable to Hispanic populations.

Using *MC1R* genotype to impact skin cancer risk behaviors in Hispanics/Latinos. The incidence of melanoma and/or keratinocyte (i.e., squamous cell and basal cell) skin cancers is trending upward among Hispanic/Latinos (H/L) living in Florida and Puerto

Rico (Gonzalez-Fernandez and Sanchez, 1999; De La Torre-Lugo et al. 2010; Hu et al. 2009). Feedback of genetic risk information has been suggested to motivate skin cancer prevention behaviors, and H/L are receptive to receiving this type information (Smit et al. 2016; Lynce et al. 2016). These activities may be important to H/L populations who have decreased awareness and risk perception of melanoma.

STUDY PURPOSE AND HYPOTHESIS

The primary objectives of this project are to:

- **Evaluate the impact of receipt of *MC1R* genotype on personal sun protection behaviors.** Determine the efficacy of a risk and prevention education session, which includes feedback of inherited *MC1R* genotype and corresponding information about genetic risk, to decrease sun exposure and increase sun protection behaviors at both short term (6 months) and long term (12 months) follow-up for our white, non-Hispanic population; for our H/L population, follow-up will occur at 3 and 9 months.
- **Evaluate the impact of receipt of *MC1R* genotypes on skin awareness and examination.** Determine the efficacy of a risk and prevention education session, which includes feedback of inherited *MC1R* genotype and corresponding information about genetic risk, to increase skin examinations at both short term (6 months) and long term (12 months) follow-up for our white, non-Hispanic population; for our H/L population, follow-up will occur at 3 and 9 months.

The secondary objective of this project is to:

- **Evaluate the impact of receipt of *MC1R* genotype on sun protection behaviors in children of study participants.** Determine whether a risk and prevention education session, which includes feedback of inherited *MC1R* genotype and corresponding information about genetic risk, can decrease the number of sunburns at both short term (6 months) and long term (12 months) follow-up in the children of white, non-Hispanic study participants; for our H/L study participants, follow-up will occur at 3 and 9 months.
- **Explore the prevalence of *MC1R* genetic variants in Hispanics living in the Tampa Bay.** We hypothesize that non-synonymous variants at *MC1R* known to be high-risk in non-Hispanic white populations of European ancestry will be readily identified among Hispanics living in the Tampa Bay area, but will occur as lower prevalence.
- **Correlate the degree of European genetic ancestry with *MC1R* variation in this Hispanic population**. We will genotype germline DNA using Ancestry Informative Markers to determine percent European (African and Asian) ancestry and correlate genomic ancestry with genetic variation in *MC1R*. We hypothesize that the prevalence of non-synonymous variants at *MC1R* observed among Hispanics living in the Tampa Bay area will decrease as the proportion of non-European (i.e. African or Asian) genomic ancestry increases.

PROJECT DESCRIPTION

For our white, non-Hispanic population we propose an intervention study to examine whether knowledge of *MC1R* genotype can lead to positive health behavior changes to reduce the risk of future development of melanoma among persons who otherwise are presumed to be at reduced melanoma risk. We posit that phenotypically low-risk individuals informed they carry *MC1R* variant(s) that place them into a high risk category will adopt melanoma risk reduction behaviors. To test this hypothesis we will randomize 1000 white, non-Hispanic patients – 500 of whom are considered at high risk and 500 of whom are considered at low risk based on *MC1R* genotyping, and all of whom report having phenotypic characteristics protective for melanoma – to receive standard risk and prevention information or to receive personalized risk and prevention information based on *MC1R* testing results. Preventive and early detection behaviors will be assessed at baseline and at 6 and 12 months post-randomization.

We also will recruit 75 to 100 individuals self-reporting Hispanic ethnicity from the USF Morsani Family Medicine clinic. Because the purpose of this secondary aim is to better understand the prevalence and distribution of *MC1R* variants in these participants, Hispanic participants will not be randomized into the intervention trial and will not complete either baseline or follow-up surveys. At this time *MC1R* genotype results will not be provided to these participants, follow up will not be required of Hispanic participants and no additional materials or questionnaires will be given to participants of this pilot study.

For our H/L populations living in Tampa Bay and Puerto Rico, we propose and intervention study in which we will recruit and randomize 800 H/L participants, 400 of whom we are considered at high risk and 400 of whom are considered at the average risk based on *MC1R* genotyping to receive standard risk and prevention information or to receive precision risk and prevention information based on *MC1R* testing results. Of the total 800 subjects, 400 H/L subjects will be identified from scheduling records of the Family Medicine and General Internal Medicine clinics of the Morsani Center at the University of South Florida, and 400 we will be recruited by our colleagues at the Ponce Health Sciences University in Ponce, PR. Therefore, a total recruitment for H/L at each site will be 400 subjects with 200 whom are considered at average risk and 200 whom are considered at high risk based on *MC1R* genotyping test results.

RESEARCH PROCEDURES

Summary. Participants in this study will be white, non-Hispanic patients with an appointment to see a physician in the Departments of Family Medicine and General Internal Medicine at the primary care clinics of the University of South Florida Health Morsani College of Medicine. We plan to approach approximately 18,500 clinic patients over a 30 month period. We will screen patients for study eligibility based on responses to questions about skin phenotypes, early detection behaviors, and past history of melanoma, and anticipate enrolling 1200 eligible study participants all of whom will sign informed consent. For our H/L population study participants will be patients with an appointment to see a physician in the Departments of Family Medicine and General Internal Medicine at the primary care clinics of the University of South Florida Health Morsani College of Medicine. Based on our ongoing recruitment, nearly 10% of

participants report being H/L. Participants (n=400) will be recruited prospectively at their clinic visit over an 18-month period.

While in clinic, individuals will complete a tablet-based (iPad application) short screening questionnaire to asses study eligibility. The screening questionnaire captures self-reported phenotypic characteristics including natural hair color at age 18 [red (including reddish-brown), blond, dark (including light brown, medium brown, dark brown, gray, and black)]; skin reaction to first strong summer sun [burn and blister, burn without blister, mild burn followed by a tan, or no burning (including no sunburn and no tan, tan with no sunburn, and no change in skin color)]; skin reaction to prolonged exposure to summer sun (no tan, light tan, or medium to dark tan), eye color [blue or gray, green or hazel, or dark (including light brown, dark brown, and black)]; and freckling (extensive, moderate, mild, or none). See ***Appendix*** for screening survey.

The eligibility screening tool also will include a short series of questions that will elicit information on performance of skin examinations. We will capture information on timing (ever and within the past 12 months) and administration (self, partner, trained professional) of skin examinations. The screening tool also will elicit information about personal melanoma history.

Patients without a personal history of melanoma will be invited to take part in the study if they i) have not had a skin examination within the past year and ii) report having naturally brown or black hair at age 18 (hair color = dark) and at least two of the three following phenotypic traits: 1) skin reaction to first strong summer sun = mild burn followed by a tan or no burning; 2) skin reaction to prolonged exposure to summer sun = medium to dark tan; 3) freckling = mild or none. In contrast, persons reporting a full body skin examination (completed by self, partner, or trained professional) within the past year, natural red or blond (fair) hair at age 18, or dark (brown or black) hair with fewer than three of these traits will be thanked for their interest and excluded from further study.

For our H/L population patients eligible for study participation will identify themselves as H/L, 18 years of age and older, able to read and speak either Spanish or English fluently; there will be no exclusions based on reported race. Individuals will be excluded from the study if they have had or completed a full skin examination over the past year, report a prior history of melanoma, report having more than one SCC, or report having more than one BCC.

After signing informed consent, a biologic sample (saliva) will be collected for the purpose of DNA extraction determination of *MC1R* genotypes. All participants who carry high risk *MC1R* genotypes and a proportion of those who carry low risk or no *MC1R* variants will be randomized to the control or intervention arm.

For our white, non-Hispanic population information on demographics and cutaneous pigmentation will be collected using a structured screening instrument. For our H/L population demographics and cutaneous pigmentation information will be collected at baseline. Information on personal sun protection behavior and skin examinations will be obtained via structured questionnaire instruments at baseline and at two follow-up times, 6 and 12 months for white, non-Hispanic population, 3 and 9 months for our H/L population. Information on potential mediators of effect will be collected at the two follow-up times using structured questionnaire instruments. The H/L intervention portion of the study is funded as a main project on Moffitt's U54 competitive renewal award for which the project timeline totals 3 years (instead of 5 years for our white, non-Hispanic population study funded under ACS). Because of the difference in the duration of the

study it was necessary to be flexible with the timing of our outcome measures; we selected 3 and 9 months follow-up for our H/L population instead of 6 and 12 months to assure two-post intervention measurement with the project timeline. Additional constructs capturing fatalism, familism and acculturation will be obtained for H/L population at baseline.

Potential participants of Hispanic ethnicity first will be identified by screening patients with scheduled appointments at the Morsani Center. Patients with clinic records indicating Hispanic will be sent an introductory study brochure and potential study participants will be recruited prospectively while in clinic. Hispanic patients will be invited to participate and a member of the study team will provide eligible patients who are interested in participating with a paper copy of the consent form, review the consent form with the patient and witness the patient's signature. The individual obtaining informed consent will also sign the consent form, and the patient will be given a copy. The consent form will include information regarding subjects' rights under the Health Insurance Portability and Accountability Act (HIPAA).

After informed consent, Hispanic participants will be asked to complete a brief questionnaire very similar to the screening questionnaire used in the main protocol and all questionnaire data will be entered into an existing database. Hispanic participants also will provide a saliva sample for isolation of genomic DNA. *MC1R* genotypes will be determined using the established pipeline created for and operational in this protocol, and Ancestry Informative Markers will be genotyped.

Study population. The target population is white, non-Hispanic patients who self-report a low phenotypic risk profile for development of melanoma. Study participants will be identified through the family or general internal medicine clinics of the USF Health Morsani College of Medicine. Patients eligible for study participation will be white, non-Hispanic, 18 years of age or older, able to read and speak English fluently, and capable of giving informed consent. Patients eligible for participation also will have a limited number of high risk phenotypes for melanoma. Participants for this research project will be recruited prospectively at their clinic visit over a 30 month period.

For H/L participants the target population will be patients who self-report as Hispanics, 18 years of age or older and are able to read and speak either Spanish or English fluently, and are capable of giving informed consent.

Consented patients with *MC1R* genotypes not selected for randomization. We will randomly select only 500 white, non-Hispanic participants from each of the *MC1R* risk categories (low and high) to participate further in our study. Therefore, some participants may receive a letter from the research team thanking them for their interest in our research project and informing them that they were not selected for further study participation. The letter will inform patients about their *MC1R* risk status and provide educational materials highlighting standardized information for the general population about melanoma, melanoma risk, melanoma prevention (i.e. sun protection and skin examination), and sun protection behaviors for children.

Randomization. For our white, non-Hispanic population we will randomize 500 participants with high risk and 500 participants with low risk *MC1R* genotypes. 50% of high risk and low risk individuals will be randomly allocated to the intervention and placebo arm (250 participants per arm) using permuted blocks, with a block size of four, and equal weighting scheme.

For our H/L population we will randomize 200 participants with high risk and 200 participants with low risk *MC1R* genotypes, with 50% of high risk and average risk individuals will be randomly allocated to the intervention and placebo arm (100 participants per arm).

Because our prior work does not indicate an increased risk of melanoma associated with low risk *MC1R* genotypes, we focus our study hypothesis on the intervention effect among persons with high risk *MC1R*. However, analysis of the efficacy of the intervention among participants in the low risk *MC1R* genotype group will enable us to assess any potential negative impact upon prevention behaviors that feedback of a 'negative' genetic test results may produce. Moreover, because the health educator will be blinded to the *MC1R* genotype status of participants randomized to the placebo arm, the addition of the low risk group affords implicit control of potential bias introduced by the health educator's knowledge of participant *MC1R* status at the time of the education session.

Placebo arm. Within one week of completion of *MC1R* genotyping (approximately 1-3 weeks after signing informed consent), a risk and prevention packet will be mailed to each participant randomized to the placebo group These printed materials will highlight customary information about melanoma, melanoma risk, melanoma prevention (i.e. sun protection and skin examination), and sun protection behaviors for children. Participants will not be given information about their *MC1R* genotype. Within two weeks of receipt of the risk and prevention mailed packet, the study health educator will contact each participant by telephone allowing the opportunity for a supplementary interactive educational session. This procedure of mailed receipt of genotype results with follow-up via telephone by a health educator has previously be demonstrated as a feasible and acceptable method for dissemination of information specific to low penetrance genetic testing (McBride et al. 2002). For participants randomized to the placebo arm, the health educator will be blinded to genotype status. Subsequent to the telephone session with the health educator, all participants in the placebo group will receive a summary letter from the research team to reinforce information contained in the original risk and prevention packet and/or covered during the health education telephone session. This letter will include the targeted date range for completion of the 6 and 12 month follow-up questionnaires. For our H/L population this letter will include the targeted date range for completion of the 3 and 9 month follow-up questionnaires. Electronic communication modalities such as e-mail will be made available to participants as requested.

Intervention arm. Within one week of completion of *MC1R* genotyping (approximately 1-3 weeks after signing informed consent), a risk and prevention packet will be mailed to each participant randomized to the intervention group. These printed materials will highlight information about natural variation in *MC1R* and its role in the development of melanoma, and they will contain personalized information about melanoma, melanoma risk and melanoma prevention (i.e. sun protection and skin examination). These materials also will include information about sun protection behaviors targeted to children. Within two weeks of receipt of the risk and prevention mailed packet, the study health educator will contact each participant by telephone allowing the opportunity for a supplementary interactive personalized educational session. This procedure of mailed receipt of genotype results with follow-up via telephone by a health educator has previously be demonstrated as a feasible and acceptable method for dissemination of information specific to low penetrance genetic testing (McBride et al. 2002). Subsequent to the telephone session with the health educator, all participants in the intervention group will receive a summary letter from the research team to reinforce information

contained in the original risk and prevention packet and/or covered during the health education telephone session. This letter may include detailed information about specific inherited *MC1R* variants if requested by the participant during the telephone health education session. This letter will include the targeted date range for completion of the 6 and 12 month follow-up questionnaires. For our H/L population this letter will include the targeted date range for completion of 3 and 9 month follow-up questionnaires. All participants in the intervention group (our white, non-Hispanic and our H/L populations) will receive a second summary letter from the research team to reinforce information contained in the original risk and prevention packet and/or covered during the telephone health education session upon completion of their final questionnaire (12 month follow-up survey for our white, non-Hispanic participants and 9 month follow-up survey for our H/L participants) along with the mailing of their final compensation gift card after study completion. Electronic communication modalities such as e-mail will be made available to participants as requested.

Encounter schedule. We expect the large majority of participants to prefer completing follow-up assessments via the Internet. We will develop a webpage and format questions so that they are easy to navigate and complete. Links to this questionnaire webpage will be e-mailed to participants at the time of the follow-up assessments. Paper questionnaires may also be mailed to study participants.

For our white, non-Hispanic population follow-up questionnaires will be sent as links to web-based surveys by e-mail and/or in hardcopy at 6 and 12 months after the prevention education session that denotes the origin of randomization, for our H/L population follow-up questionnaires will be sent as links to web-based surveys by e-mail and/or in hardcopy at 3 and 9 month after the prevention education session that denotes the origin of randomization The follow-up assessments measuring skin self-examinations and sun protection behaviors will be identical to those given at baseline. The follow-up questionnaires also will assess cancer distress that may be attributed to receipt of explicit information about melanoma risk and/or *MC1R* genotype. Reminder communications will include a combination of telephone, email, text and mail.

Baseline and outcome measures*.** The baseline questionnaire administered via tablet (iPad) will be completed in the clinic in conjunction with the patient's visit, or will be filled out after the visit and returned via postal mail to the project team in a pre-paid envelope. In the baseline questionnaire the respondents are asked how they prefer to be contacted in future interactions either by e-mail or postal mail. All follow-up questionnaires and information will be available both as web-based and paper versions. See ***Appendix for baseline questionnaire.

Demographic variables. A number of demographic variables will be obtained such as age, gender, educational level. We also will inquire about additional background variables such as place of birth and family history of melanoma, other non-melanoma skin cancers, and other cancers.

Early detection and prevention measures. Information on sun exposure, skin examinations and sun protection behaviors will be collected using a published questionnaire with questions adapted to the specific needs of the proposal (Glanz et al. 2008). The self-reported sun exposure questions previously have been validated (Glanz et al. 2010).

Hypothesized mediators*.* To determine the influence of health beliefs (i.e. PMT constructs), cancer-related distress and worry, health literacy and numeracy as potential mediators of behavior change, we will measure these factors at baseline and follow-up.

Health literacy. Single Item Literacy Screener items will be used to assess participants' health literacy (Morris et al. 2006). We will use three items reflecting 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. Each is measured on a 5-point scale ranging from none of the time to all the time.

PMT constructs of vulnerability, severity, response efficacy, and self-efficacy will be assessed using previously developed measures specific to genetic risk for melanoma (Azzarello et al. 2006, Azzarello et al. 2007). To assess perceived susceptibility, participants will be asked to rate the chance they would: develop melanoma during their lifetime (likely/unlikely), and develop melanoma relative to other persons of similar age (1 = well below average to 5 = well above average). A total self-efficacy for skin cancer prevention behaviors score (Cronbach's $\alpha = 0.78$) will be derived by summing ratings (1 = Not at all capable to 4 = Extremely capable) to four items (e.g. How capable do you feel that you can limit sun exposure between 10am and 4pm). A total response efficacy for skin cancer prevention behaviors score (Cronbach's $\alpha = 0.85$) will be derived by summing ratings (1 = Not at all important to 6 = Extremely important) to four items (e.g. How important do you think using sunscreen with sun protection factor 15 or higher helps to reduce my chances of developing melanoma).

Cancer distress will be evaluated using the 15-item Impact of Event Scale (IES) to assess intrusive (Cronbach's $\alpha = 0.78$) and avoidant ($\alpha = 0.82$) responses to stressful events, in this case developing melanoma (Horowitz et al. 1979, Kasparian et al. 2010). Participants rate the frequency of intrusive and avoidant cognitions and behaviors regarding their melanoma risk using a 4-point frequency scale (0=not at all to 4=often). A total score ≥ 40 is considered indicative of a significant stress response.

Cancer worry will be assessed using a 3-item adaptation of the Lerman Cancer Worry Scale that has been used in prior studies of those at increased risk for melanoma (Lerman et al. 1994). Participants will be asked how often in the past month they reported thinking about their own or chances of developing melanoma and how often these thoughts had affected their mood as well as how concerned they were about the possibility of developing melanoma (1=not at all concerned to 5=very concerned). These items will be averaged to form a melanoma worry score (Cronbach's $\alpha = 0.62$-0.67) (Aspinwall et al. 2013).

For our H/L study population we will also measure fatalism, familism and acculturation at baseline.

Acculturation will be assessed using variables that include birthplace and time lived in the U.S. Participants will be asked how many years they have lived in the U.S as well as how many years have they lived outside of the U.S. and for how long (6 months or greater, less than 6 months, name of the country they lived in). This measure was adapted from Berrigan et al. (Berrigan et al. In Press).

Familism examines attitudes regarding participants' families using an 18-item attitudinal familism scale (Lugo et al., 2003). Participants will be asked about their personal beliefs about family (1=strongly disagree to 4=strongly agree). The following main four components of attitudinal familism will be measured: the family comes before the individual, familial interconnectedness, familial reciprocity in times of need, and familiar honor (Lugo et al., 2003).

Fatalism will be assessed using a 7-item scale (Jensen et al., 2014) that measures fatalistic views concerning undertaken cancer prevention behaviors and a 6-item scale (Jensen et al., 2014; Powe & Finnie, 2003) that measures fatalistic views about cancer treatment. These two scales are currently used in a combined fashion in an ongoing study conducted by our study consultant (Jennifer Hay, Ph.D., Memorial Sloan-Kettering Cancer Center), and we have adopted this working version. Participants will be asked questions regarding their fatalistic views concerning both cancer prevention and treatment (1=agree and 2=disagree).

Follow-up assessments. To capture changes in early detection and prevention items over time, we will re-administer the 14-item measure for adults and 12-item measure for adults reporting for children at 6 and 12 months for our white, non-Hispanic population and at 3 and 9 month for our H/L population. A 12 month follow-up assures that all white, non-Hispanic participants are under observation for a full year, thus implicitly allowing all participants to experience both winter and summer months during which preventive behaviors may differ. We also will ask all participants to complete instruments assessing potential mediators at both follow-up times. The questionnaires used at follow-up will be e-mailed to participants as links to a web-based interface and/or mailed along with prepaid return envelopes.

Participant retention. To enhance retention at the 6 and 12 month time points for our white, non-Hispanic population and at 3 and 9 month for our H/L population, patients randomized to either the intervention or placebo arm will receive a series of two gift cards, each in the amount of $20. The first will be mailed to participants along with the summary letter after the health education session. The second will be sent via U.S. mail after completion of the 12 month follow-up questionnaire for our white, non-Hispanic participants and after completion of the 9 month follow-up questionnaire for our H/L participants. Consented patients with low risk *MC1R* genotypes who are not selected for randomization will receive one $10 gift card to be included in the mailing that conveys their ineligibility for further study participation.

We also will supplement monetary incentives for questionnaire completion with reminder post cards mailed the month preceding study assessments and birthday cards, which we have used in previous studies involving recruitment and retention of individuals at increased genetic risk for cancer in which telephone and in-person genetic counseling, disclosing test results, and periodic follow up assessments were undertaken for study participants (Pal et al. 2011, Christie et al. 2012, Vadaparampil et al. 2012). All communications will include postage paid response cards to update contact information. We conservatively estimate study attrition over the follow-up period at 20%.

Intervention risk and prevention materials feedback. We will use Learner Verification (LV) (Doak, Doak et al. 1998) to refine and finalize our genetic risk feedback materials. LV focuses on five key elements: 1) attraction, 2) comprehension, 3) self-efficacy, 4) cultural acceptability, and 5) persuasion (i.e., intentions to pursue GC). LV needs ~6 individuals per each of two iterative steps. For our white, non-Hispanic population we will recruit 12 patients (n=6 per step; n=3 per risk feedback version) to uncover issues with the format or content and ensure the content is consistent with audience characteristics, (e.g., literacy level). For our H/L population we will recruit 12 patients (n=6 in Puerto Rico and in Tampa Bay) to uncover issues with the format or content and ensure the content follows audience characteristics. After obtaining informed consent, we will use LV concepts and the brief interview guide to elicit

participant feedback on the materials. The interviews will be recorded and transcribed. To assess the Learner Verification elements, a simple tabular representation of responses to each question is considered a sufficient method for identifying key areas for improvement (Doak, Doak et al. 1996). Transcribed texts from the individual interviews will be converted into tabular format according to question types in an Excel spreadsheet. After the first round of interviews, study team members will review these tabulations to identify areas for improvement in the genetic risk feedback materials and make changes to materials that will be reviewed in the subsequent round. After the second round of interviews are completed, transcribed text will again be summarized in a tabular format to guide final changes that will be made to the materials. The eligibility criteria for participating in the LV interviews will be same as for the main portion of the study. Each participant will receive a $20.00 Target gift card at the end of the interview/discussion session for their participation.

Translation of study materials for H/L population. The precision genetic feedback materials will be adapted from Spanish versions used in NCI-funded investigation of utility and reach of precision genomic testing for melanoma (PI, J. Hay; R01CA181241). We are familiar with these educational materials as the English versions were adapted for use for the ongoing IMPACT-ME intervention study at MCC among white non-Hispanic participants. We will team with the Community Advisory Panel (CAP) of the Partnership Outreach Core to transcreate these materials to ensure the comprehension and cultural relevance to the H/L population living in Tampa Bay and Puerto Rico (Rivera et al. 2016). The CAP comprises medical professionals, cancer survivors, and/or community health workers with experience working with the H/L community; the CAP has assisted with the transcreation of outreach and research materials from English to Spanish for project, services and cores related to the Partnership. We will work closely with a process, we will be mindful of recommendations for development of general and genetic-specific health education materials such as using pictures, health numeracy and using pictographs to indicate quantitative information (e.g., risk), attention to general health literacy and genetic health literacy, visual appeal. We will also use an iterative process for the translation of introductory letters and leaflets, and baseline and follow-up instruments into Spanish. Here, we first will use a certified translator to create a Spanish language version of these items. All translated instruments will be reviewed and feedback obtained. We will then engage the CAP and complete the Learner Verification in parallel with the educational materials.

Intervention monitoring. We will assure consistency of intervention by monitoring education sessions over the course of the study. Specifically, Drs. Kanetsky and Vadaparampil will review audio-recordings of 5% of all education sessions and will provide feedback results to the project health educator. Study subjects participating in recorded sessions will provide consent. We also will assess participant reactions to study materials including the standardized information given to participants in the placebo arm and personalized information given to participants in the intervention arm. Study materials will be rated on a 5-level Likert scale (1 = Not at all; 5 = Very) on the following features: easy to understand, informative, interesting, personally relevant, attractive, and confusing.

The timeline for our white, non-Hispanic population research is 5 years. The anticipated timing of various project components is given in the Table below.

Study timeline.	Year 1		Year 2		Year 3		Year 4		Year 5	
	Q1/Q2	Q3/Q4	Q5/Q6	Q7/Q8	Q9/Q10	Q11/Q12	Q13/Q14	Q15/Q16	Q17/18	Q19/Q20
IRB & develop patient packets	•									
Develop web-based interface	•									
Develop counseling packets	•									
Staff training and piloting	•									
Patient recruitment and consent		•	•	•	•	•				
Baseline questionnaire		•	•	•	•	•	x			
MC1R genotyping		•	•	•	•	•	x			
Risk prevention counseling		•	•	•	•	•	x			
Follow-up questionnaire (6 mo)			•	•	•	•	•	x		
Follow-up questionnaire (12 mo)				•	•	•	•	•	x	
Data cleaning							•	•	•	
Data analyses							•	•	•	•
Abstracts and manuscripts								•	•	•

x indicates timeline of augmented patient recruitment, if necessary.

The timeline for our H/L population research study is 3 years. The anticipated timing of various project components is given in the Table below.

Study timeline.

	Year 1		Year 2		Year 3	
	Q1/Q2	Q3/Q4	Q5/Q6	Q7/Q8	Q9/Q10	Q11/Q12
IRB approval	•					
Transcreate Spanish study materials	•					
Adaptation of existing web-based interface	•					
Staff training and piloting	•					
Patient recruitment and consent	•	•	•			
Baseline questionnaire	•	•	•			
MC1R genotyping	•	•	•			
Health educator phone call	•	•	•	•	•	•
Follow-up questionnaire (3 mo)		•	•	•		
Follow-up questionnaire (9 mo)			•	•	•	
Data cleaning			•	•	•	
Data analyses					•	•
Abstracts and manuscripts					•	•

SELECTION OF SUBJECTS

The number of samples will be 1200 saliva DNA collected using Oragene kits.

The participants/samples will be selected from among approximately 18,500 clinic patients see at Morsani clinics over a 30 month period. We will screen these patients for study eligibility based on responses to questions about skin phenotypes, early detection behaviors, and past history of melanoma; and we anticipate enrolling 1200 eligible study participants. For our H/L population the participants/samples will be selected from among nearly 10% of participants that report being H/L based on our ongoing recruitment over an 18 month period. We will screen these patients for study eligibility based on responses to questions about early detection behaviors, past history of melanoma and past history of more than one SCC and BCC.

Inclusion Criteria for participant selection for our white, non-Hispanic population includes the following:
Enrolled study participants will be at least 18 years old without a personal history of melanoma; children between the ages of 18-21 will be eligible to participate. The study sample is anticipated to represent roughly equal numbers of men and women. Study participants will not have had a skin examination within the last year and will be of European ancestry. The study sample will be limited to non-Hispanic whites because i) skin type is the overwhelming risk factor for cutaneous melanoma resulting in very low incidence of this disease among persons who are black, Asian, Native American or

Pacific Islander, and ii) the prior genetic investigation upon which this application is based was undertaken in a non-Hispanic white population (Kanetsky et al. 2010). Thus at this time, inference of genetic risk attributable to *MC1R* variants is unknown for individuals not identifying as non-Hispanic white eliminating any direct inference of the proposed intervention to a non-Hispanic white population.

For our H/L population inclusion criteria for participant selection includes the following:

Enrolled study participants will be at least 18 years old, self-report Hispanic ethnicity (there will be no exclusions based on reported race), without a personal history of melanoma and without a personal history of more than one SCC and/or BCC; children between the ages of 18-21 will be eligible to participate.

Exclusion Criteria for our white, non-Hispanic population:
Children under the age of 18.
Participant whose medical records or self-report indicate any race or ethnicity identification aside from white, non-Hispanic.
Participants reporting sun-sensitive phenotypes.
Participants having had a skin examination within the past year.

Exclusion Criteria for our H/L population:

Children under the age of 18

Participant whose medical records or self-report indicate an ethnicity aside from Hispanic.

Participants having had a skin examination within the past year.

Participants with a personal history of melanoma and/or more personal history of more than one SCC and/or BCC.

Primary Outcome of the Study:

Primary outcomes will be measured using an adapted version of a published survey assessing measures of sun exposure and sun protection (Glanz et al. 2008) (see ***Appendix***).

For Aims 1 and 2, the 14-item measure for adults (Section A) will be used. Section A is completed by the study participant and elicits responses about his/her own sun protection and skin examination behaviors including: average number of hours spent outside during weekdays and weekend days in the summer; number of red or painful sunburns during the past 12 months; frequency of sun protection behaviors when outside in the summer sun; frequency of intentional tanning; color of untanned skin; and skin examinations by a health professional or by the study participant him/herself or his/her partner.

For Aim 1, the primary outcome of interest is average number of hours spent in the sun per week between 10am – 4pm. This measure will be a weighted average of the first two questions on the survey asking about number of hours spent outside during the hours of 10 to 4 on weekdays (Section A, Q1) and on weekend days (Section A, Q2). We will tailor the timeframe of Q1 and Q2 given in Glanz et al. to fit our Aim and our timeline (Glanz et al. 2008). At baseline the timeframe will be “in the past 12 months”; and for our white, non-Hispanic population at the 6 and 12 month follow-up surveys and

at 3 and 9 month for our H/L population, the timeframe will be “in the past 6 months” for our white, non-Hispanic populations and “in the past 3 months” for our H/L population.

For Aim 2, the outcome of interest for this aim is having a skin examination (yes/no) assessed at the 6- and 12-month follow-up visits for our white, non-Hispanic population and at 3 and 9 month follow-up visits for our H/L population. This outcome will be a composite of examinations performed by a clinician (e.g. primary care doctor or dermatologist; Section A, Q11) or those completed by oneself or one’s partner (i.e. self-skin examination; Section A, Q13). We will tailor the suggested text of Q11 and Q13 given in Glanz et al. to fit our Aim and our timeline (Glanz et al. 2008). Q11 will be revised to read “In the past [time] months, have you had …” (compared to “Have you ever had …” as it currently reads). We will tailor the timeframe to correspond to the baseline, 6 or 12 month survey for our white, non-Hispanic population and at 3 or 9 month survey for our H/L population: at baseline the timeframe will be “in the past 12 months”; at the 6 and 12 month follow-up surveys, the timeframe will be “in the past 6 months” for our white, non-Hispanic population and “in the past 3 months” for our H/L population. In order to address the potential of a ceiling effect, we will ask participants who respond ‘yes’ to having had a skin examination in the past 6 months (white, non-Hispanic population) and3 months (for our H/L population) the month and year of examination and whether the examination occurred at the Morsani Family Medicine or General Internal Medicine clinics. The outcome will be operationalized such that responding ‘yes’ to questions regarding completion of a skin examination by a clinician or by oneself or one’s partner will be considered a ‘yes’ response for skin examinations. Thus, this outcome is operationally a binary response (e.g., yes/no in the past 6 months (for our white, non-Hispanic participants) and in the past 3 months (for our H/L participants)) measured at the 6- and 12-month follow-up visits for our white, non-Hispanic population and at 3 and 9 month follow-up visits for our H/L population.

For Exploratory Aim 3, the 12-item measure for children age 10 years or younger as reported by the study participant (Section B) will be used. Study participants with at least one child 10 years of age or younger will complete Section B, and those participants with more than one child within this age range are instructed to answer questions in this section thinking about the oldest child. Section B elicits responses about sun protection behaviors of the child, including number of red or painful sunburns over the past year for white, non-Hispanics and over the past 9 months for our H/L populations.

Since intermittent sunburns in adolescence are strongly associated with future melanoma risk (Armstrong et al. 1993, Gandini et al. 2005), the outcome of particular interest for our exploratory aim is the number of red or painful sunburns that lasted a day of more over the past timeframe. This outcome is measured by Section B, Q5, with a range of possible responses of 0 through 5 times (5 indicating 5 or more red or painful burns). We will tailor the timeframe to correspond to the baseline, 6 or 12 month survey for white, non-Hispanic participants and at baseline, 3 or 9 months survey for H/L participants).

STATISTICS

There will be no merging of data between the white non-Hispanic study population and

the H/L study population data. We will conduct mutually exclusive analyses within each of these two study populations.

Non-Hispanic study population

For our white, non-Hispanic population, the number of participants, 500 with high risk *MC1R* genotypes required to participate in this study was based upon the power calculations below.

Study power, Aim 1. We determined that randomizing 500 participants with high risk *MC1R* variants (250 each to the intervention and placebo arm) ensures 80% power to detect mean differences in hours of sun exposure of 0.17, 0.50 and 0.84, respectively, when the estimated standard deviation of the observed means is equal to 1, 3 and 5, respectively, when comparing participants with high risk genotypes who are randomized to intervention to participants with high risk genotypes who are randomized to placebo. These calculations are based on two-sided, alpha=0.05 level tests assuming a conservative auto-correlation equal to 0.1 to account for the repeated measures of participants over time, and a conservative 20% study attrition.

Study power, Aim 2. We estimate a 20% incidence of having a skin examination within the past 12 months among participants on the placebo arm who received only standard risk and prevention information. We also conservatively estimate study attrition at 20%. Using these estimates, we determined that randomizing 500 participants with high risk *MC1R* variants (250 per study arm) ensures 80% power to detect an odds ratio of at least 1.8 when comparing participants with high risk genotypes who are randomized to intervention to participants with high risk genotypes who are randomized to placebo for the skin examination (yes/no) outcome. These calculations are based on two-sided, alpha=0.05 level tests and vary the proportion of skin examinations in the placebo group from 15-36% to be consistent with the range of possible values noted in the published literature.

Because we do not know the proportion of study participants who will have children 10 years of age or younger, we do not report study power for Aim 3 and consider this aim as exploratory at this time.

For our H/L populations the total number of participants, 400 with high risk *MC1R* genotypes (200 of whom will be recruited locally and 200 recruited in PR) required to participate in this study was based upon the power calculations below.

Hispanic/Latino study population

For our H/L populations the total number of participants, 400 with high risk *MC1R* genotypes (200 of whom will be recruited locally and 200 recruited in PR) required to participate in this study based upon the power calculations below.

Study power, Aim 1. Randomizing 400 participants with high risk *MC1R* variants (200 each to the intervention and control arm) ensures 80% power to detect mean differences in hours of sun exposure comparable to a small-medium effect size (Cohen's d=30),

when comparing participants with high-risk genotypes to intervention versus participants with high-risk genotypes randomized to control.

Study power, Aim 2. We estimate a 20% incidence of having a skin examination with the past 9 months among control participants, with a range of 15% to 35%, and estimate study attrition of 20%. Using these estimates, we determined that randomizing 400 participants with high-risk *MC1R* variants (200 per study arm) ensures 80% power to detect an odds ratio of at least 1.95 to 1.73 when comparing participants with high-risk genotypes randomized to intervention versus those randomized to control for the skin examination (yes/no) outcome.

General approach. All analyses will be done within SAS, version 9 or later, primarily using PROC UNIVARIATE, FREQ and GENMOD. In the primary analyses, we will use an intention-to-treat (ITT) approach in which participants are analyzed in their randomized conditions regardless of the number of interventions or number of follow-up assessments they complete. Two-sided tests will be used for all hypotheses. We will assess the data for missing and out-of-range values with basic statistical procedures, including univariate statistics and graphs (histograms, box and whisker plots, scatter plots, and Q-Q plots). We will investigate data quality and integrity before any statistical modeling to ensure unbiased estimation.

The primary aim of this proposal is to test for significant ITT differences in the proportion of study subjects participating in skin prevention behaviors over the 12-month follow-up period by comparing those who receive a risk and prevention education intervention that includes feedback of *MC1R* genotype to those who receive a risk and prevention education session that includes only standard information. Our two primary outcomes of interests are (1) the average hours per week (weekdays and weekend) spent outside between 10am – 4pm; and (2) the completion of a full body skin examination for skin cancer (yes/no) by self, partner or clinician.

Aim 1. We will use a linear GEE regression model with main effects for the intervention (standard risk and prevention plus genetic education versus standard risk and prevention education only), time, and the interaction terms between the intervention and time. The interaction term will be the main test of interest as it assesses average departure from the slope due to the intervention. We will include other covariates related to dropout or involving potential baseline imbalances between the intervention groups as appropriate, as well as month of completion of the questionnaires to account for seasonality.

We will perform analyses to test whether participants and eligible non-participants differ on basic demographic variables using cross-sectional logistic or linear regression models for binary or continuous factors, respectively. We will perform attrition analyses to determine whether participants and dropouts differ on key variables. We will include these factors in the above ITT model to see if they affect the results. A few randomly missing observations have only a slight impact on power and do not introduce bias. However, large numbers of non-randomly missing values can bias results.

We also will conduct mediator analyses to determine whether the effect of the intervention on prevention behaviors is explained by health beliefs or cancer distress. We will use a series of models to examine whether (a) the intervention is predictive of the mediator, (b) the mediator is predictive of prevention behaviors in a multivariable model controlling for the intervention, and (c) the addition of the mediator to a

multipredictor model for prevention behaviors attenuates the estimated coefficient for the intervention. To assess mediation effects, we will use the approaches by Imai et al., which are available through add-on packages to existing statistical software (such as R and STATA) (Imai et al. 2010, Imai et al. 2012). Similar to the method of Preacher and Hayes (Preacher et al. 2008), their methods employ bootstrapping to estimate mediating causal effects . These analyses will be used to estimate the direct effect of the intervention via pathways other than through the posited mediator, its indirect effect via the mediator, and the degree of mediation. This approach will allow us to quantify the effect of the intervention due to the potential mediator (if any), which can inform future interventions or prevention strategies.

Aim 2. Hypothesis testing for the binary outcome of full-body examination (yes/no) will follow the general analytic outline used in Specific Aim 1. This outcome will be modeled using the logistic framework of the GEE approach (i.e. specifying a logit link function), which properly accounts for the induced correlation from the repeated measures on participants over time, to assess ITT differences. These ITT differences comparing the probability of skin examinations will be presented as odds ratios with corresponding 95% confidence intervals where models will include main effects for intervention (standard risk and prevention plus genetic education versus standard risk and prevention education only), time (0, 6, and 12 months), and interaction term between the intervention and time. The interaction term will be used to test for possible differences in effects over time in the two study arms as the main test of interest. In addition, the logistic GEE model will contain baseline covariates and variables related to study participation and/or attrition as appropriate.

Exploratory Aim 3. We will use the GEE Poisson or ordinal regression models as appropriate with main effects for the intervention, time, and interaction term between the intervention and time, and will adjust for date of study enrollment to account for seasonality. Specifically, we are interested in estimating the intervention's efficacy in reducing the average number of red or painful sunburns in children.

All statistical analyses will be conducted by a member of the Biostatistics Core under the direction supervision of Dr. Hui-Yi Lin.

Analyses among individuals with low-risk *MC1R* genotypes will be conducted in a similar fashion to those detailed above. Because we do not expect to see ITT differences in prevention behaviors comparing those who receive a risk and prevention education intervention that includes feedback of *MC1R* genotype to those who receive a risk and prevention education session that includes only standard information among the low-risk group, power analyses are omitted.

Pilot study Aim 1. The overall prevalence of *MC1R* genotypes will be calculated with corresponding 95% confidence intervals.

Pilot study Aim 2. Genotyping quality control for each AIM will first be assessed using standard sample-level and SNP-level metrics. Using markers and among samples passing quality control, individual genetic ancestry will be estimated using Structure. Prevalence of genotypes within percentile categories of European ancestry determined from AIMS and within categories of self-reported sun-resistant phenotype characteristics (where available) will be determined. The precision of prevalence estimate may be limited for variants occurring at low frequency. The current study sample size is constrained by available pilot funding, but it is expected that estimates obtained in the current study will provide preliminary data supporting future melanoma research among Hispanic populations in the Tampa Bay area and Puerto Rico.

DATA COLLECTION

We will collect selected Protected Health Information (PHI), including but not limited to Name, Address, Age, MRN, and SSN, for the purpose of patient identification, tracking, and contact. After the conclusion of the study, any PHI solely used for patient identification and tracking (e.g. MRN and SSN) will be permanently deleted.

Data coordination and management will capitalize on existing experience and available infrastructures of the Moffitt Cancer Informatics Core (CIC) and Research Information Technology (RIT) division. In coordination with Drs. Kanetsky and Vadaparampil, the CIC and RIT will develop a data management system, including tablet-based applications, for storage of data and tracking of participant completion status. They will oversee creation of the web-based follow-up questionnaires and implement an automated messaging system triggered by individual patient trajectories through the project timeline. Reports will be generated by the CIC and RIT for review by the study team to assure timely completion of the study goals.

Data collection will be performed by research study investigators and staff.

All identifying data will be stored in secured and password protected files separate from all other research information, which will be identified by study identification number alone. The study database, into which information about participant contact and data from all surveys and genotype will be entered, will be hosted on secure computing servers developed by the Cancer Informatics Core and the Research Information Technology Department and will be restricted to only those individuals who are authorized to work on the study. Individual user accounts with passwords will be used to restrict access to the database. Specific privilege assignments within the database will also be employed to limit the types of functions that authorized users can perform to those functions that are appropriate for their role in the study.

RISKS

We believe there is minimal risk to study participants. There are no physical or medical risks or side effects associated with taking part in this study. Questionnaire instruments designed to assess skin protection behaviors do not include sensitive items, although some participants may feel a sense of responsibility while reporting the behaviors of their child under the age of 10 (for those participants with young children). There is no risk associated with giving a saliva sample. However, loss of confidentiality concerning risk and prevention behaviors or *MC1R* genotyping is always a risk to study participants, albeit we believe a negligible one.

There also may be emotional risk associated with feedback of genotype information including increased stress and worry, and in its most severe state suicide, although this would be unlikely. Emotional risk associated with feedback of genetic information also may manifest as feelings of stress and worry that one's child may develop melanoma. It is possible that stress and confusion may arise among persons with indeterminate or failed genetic tests, although we believe this scenario also is unlikely.

Participants in the study will be assured of strictest confidentiality. Special attention will be paid to the collection and storage of personal health information (name, address, phone number, etc.) to be used predominantly for tracking and follow-up purposes.

Of particular note, no identifying information will be collected relating to children of enrolled participants, and the study team will not attempt to identify said children under 18 years old.

Similarly, all biologic samples (saliva, storage vials, sequencing plates) will be labeled solely with the study identification number and date of collection; and genotype data will be stored linked only to the study identification number. These are all standard procedures practiced in the Moffitt Cancer Center Tissue and Molecular Genomics Cores.

All identifying data will be stored in secured and password protected files separate from all other research information, which will be identified by study identification number alone. The study database, into which information about participant contact and data from all surveys and genotype will be entered, will be hosted on secure computing servers developed by the Cancer Informatics Core and the Research Information Technology Department and will be restricted to only those individuals who are authorized to work on the study. Individual user accounts with passwords will be used to restrict access to the database. Specific privilege assignments within the database will also be employed to limit the types of functions that authorized users can perform to those functions that are appropriate for their role in the study. Any publications or presentations resulting from this work will not identify participants by name, but will present only aggregate data. In the unlikely event of loss of confidentiality of *MC1R* genotype information, the Genetic Information Nondiscrimination Act (GINA) of 2008 protects individuals from being treated unfairly based on the inherited genetics, and thus prevents discrimination by health insurers and employers.

Prior to initiation of participant recruitment, research team members will be trained by a member of the Moffitt Psychosocial Team to recognize differences between participants experiencing a normal range of emotions versus those that are visibly distressed and when patient referral is needed. Participants exhibiting high levels of stress or cancer worry will be referred to Dr. Roetzheim for consultation. We will be able to capture change in a study participant's stress and cancer worry potentially attributable to the intervention by comparing responses of survey questions at either 6 or 12 months and baseline. Patients demonstrating a large increase in stress or worry will be identified by the research team, contacted, and offered the opportunity to further discuss their melanoma risk and mechanisms for risk reduction with Dr. Roetzheim. If appropriate, patients will be provided suggestions and additional sources for professional help.

Potential benefits of the proposed research differ by randomization assignment. For study participants randomized to receive intervention risk and prevention education, the potential benefits of the proposed research are improved preventive behaviors against melanoma. These behaviors, if sustained, can decrease risk of developing melanoma and/or increase the likelihood that a melanoma is detected at an early stage. While study participants randomized to receive standard risk and prevention education may also benefit from receipt of traditional prevention materials and having interaction with the project educator, we anticipate that any increase in preventive behaviors will be inferior to those observed among participants randomized to the intervention arm. Thus at the conclusion of the study, we will provide personalized prevention information including *MC1R* genotype including its associated risk of melanoma to all participants randomized to receive standard risk and prevention education (akin to information received by participants randomized to the intervention arm).

CONSENT PROCESS

For our white, non-Hispanic population we expect to have to screen about 18,500 patients in order to identify our target population of 1200 for enrollment into our randomized behavioral intervention study. For our H/L population we expect to screen about 10% of participants that report being H/L from the over 25,000 patient visits per year based on our ongoing recruitment of our white, non-Hispanic population in order to identify our target population of 400 for enrollment into our H/L population randomized behavioral intervention study.

Because of the additional burden of obtaining informed consent on over 17,300 individuals who will not contribute to testing our study hypotheses, we will request a waiver of informed consent for the screening process.

For our white, non-Hispanic population we plan to collect the following data under a waiver of informed consent:

- Age
- Sex
- Natural hair color at age 18
- Skin reaction to first strong summer sun
- Skin reaction to prolonged exposure to summer sun
- Natural eye color
- Freckling
- Ever had a skin examination
- Skin examination within the past 12 months
- If yes, mode of administration of skin examination
- Personal history of melanoma

For our H/L population we plan to collect the following data under a waiver of informed consent:

- Age
- Ever had a skin examination
- Skin examination with the past 12 months
- If yes, mode of administration of skin examination
- Personal history of melanoma
- Personal history of more than one SCC
- Personal history of more than one BCC

If eligible, screened patients also will be asked for the following data under the waiver of informed consent in order to streamline the process of obtaining the electronic version of the study informed consent:

- Name
- Address
- Phone number
- Email address
- Date of birth

On the tablet-based screening survey and prior to asking specific screening questions, we will include text explaining the screening survey. This text will convey that depending upon an individual's responses, he or she may be further asked to participate in the full research protocol. We anticipate real-time processing of screening eligibility allowing for seamless transition for participants who are study-eligible.

All eligible screened patients will provide full informed consent (and will be given a copy of the consent for their records) before continuing. The study staff will assure that every participant understands the various study components including the implications of randomization, completion of the baseline questionnaire, biospecimen collection, scheduling and participating in a risk and prevention education session within 1-2 months of study enrollment, completion of up to two follow-up surveys, and study appreciation in the form of two gift cards.

Potential participants first will be identified by screening patients with scheduled appointments at the Morsani Center. Patients with clinic records indicating white race, non-Hispanic ethnicity as well as Hispanic ethnicity regardless of race, will be sent an introductory study brochure. Potential study participants will be recruited prospectively while in clinic. Clinic patients will be approached by the study team for further eligibility screening via survey instrument for our white, non-Hispanic population based on self-reported race/ethnicity, self-reported phenotypic characteristics, and self-reported skin prevention behaviors and for our H/L population based on self-reported ethnicity and self-reported skin prevention behaviors . All eligible patients will be invited to participate. A member of the study team will provide eligible patients who are interested in participating with either a written or electronic version of the consent form, review the consent with the patient, and witness the patient's signature. The consent form will include information regarding subjects' rights under the Health Insurance Portability and Accountability Act (HIPAA). The information to be communicated will include the goals of the study, the fact that assignment to receive standard vs. genetic risk and prevention education is random, that their participation is purely voluntary and not part of their medical care, that they lose none of their rights regarding medical care, that they can withdraw from the study at any time, that they will be kept informed if there are changes in care or standard-of-care that would affect their willingness to participate, and the fact that they will be compensated for their participation. The patient will be asked to consent using a tablet with an electronic signature capture or a paper version of the consent. The individual obtaining informed consent will also sign the consent form, and the patient will be given a copy. The electronic document image of the signed consent form is converted to a secure PDF file representative of such and stored in a secure location on the Moffitt network. In circumstances when the electronic system is inoperable, the

signed paper consent will be copied for the patient and stored in a secure environment at Moffitt.

GENETIC TESTING

Biospecimen collection and baseline questionnaire. Once the patient provides informed consent, he/she will provide a saliva sample for isolation of genomic DNA. Oragene® (DNA Genotek, Inc.) kits will be used for saliva collection, and saliva samples will be delivered to the Moffitt Tissue Core for processing.

***MC1R* genotyping.** Saliva samples will be processed for the isolation of genomic DNA in the Moffitt Tissue Core according to the manufacturer's instructions. Isolated DNA will be delivered to the Moffitt Molecular Genomics Core for complete exonic sequencing of *MC1R* (1 exon, 961 bp) to identify all existing variants using published methods (Kanetsky et al. 2010). Dr. Kanetsky has vast experience with sequencing this locus, having genotyped and interpreted *MC1R* sequencing output for over 5000 samples (Kanetsky et al. 2006, Kanetsky et al. 2010).

Using observed *MC1R* genotypes, we will identify our target high (genetic) risk population based on criteria set forth in our previous work (Kanetsky et al. 2010). We will define a high risk *MC1R* variant as any of the following: p.D84E, p.R151C, p.D160W, and p.D294H. We also consider the g.86_87insA, g.411delC, and g.537_538insC insertion/deletion variants, the p.Y152X and p.R163X nonsense variants as high risk based on their effect (premature truncation) on the receptor protein, although we anticipate observing only a handful of these variants given their low prevalence in the general population (Kanetsky et al. 2006). Low risk *MC1R* variants include any other observed non-synonymous variation distinct from those variants listed above. Consistent with our prior findings, we define the high risk group as persons who carry at least one high risk *MC1R* variant or two low risk variants (in the absence of a high risk variant) (Kanetsky et al. 2010). We define the low risk group persons who carry only one low risk or no *MC1R* variant (i.e. all remaining individuals).

Ancestry Informative Markers. For Hispanic participants, a set of 106 SNPs that discriminate indigenous American, African, and European ancestry (also known as ancestry informative markers or AIMs) will be used to estimate the proportion of genetic ancestry in study participants. The SNPs chosen maximize information for more than one ancestral population pairing, with a large difference in allele frequency between ancestral populations and the ancestry informative markers are widely spaced throughout the genome and have a well-balanced distribution across all 22 autosomal chromosomes. Genotyping will be done using a multiplex PCR coupled with single base extension methodology with allele calls using a Sequenom analyzer.

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