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The melanoma genomics managing your risk study: A protocol for a randomized controlled trial evaluating the impact of personal genomic risk information on skin cancer prevention behaviors

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ABSTRACT

Background: Reducing ultraviolet radiation (UV) exposure and improving early detection may reduce melanoma incidence, mortality and health system costs. This study aims to evaluate the efficacy and cost-effectiveness of providing information on personal genomic risk of melanoma in reducing UV exposure at 12 months, according to low and high traditional risk.

Methods: In this randomized controlled trial, participants (target sample = 892) will be recruited from the general population, and randomized (1:1 ratio, intervention versus control). Intervention arm participants provide a saliva sample, receive personalized melanoma genomic risk information, a genetic counselor phone call, and an educational booklet on melanoma prevention. Control arm participants receive only the educational booklet. Eligible participants are aged 18–69 years, have European ancestry and no personal history of melanoma. All participants will complete a questionnaire and wear a UV dosimeter to objectively measure their sun exposure at baseline, 1- and 12-month time-points, except 1-month UV dosimetry will be limited to ~250 participants. The primary outcome is total daily Standard Erythemal Doses at 12 months. Secondary outcomes include objectively measured UV exposure for specific time periods (e.g. midday hours), self-reported sun protection and skin-examination behaviors, psycho-social outcomes, and ethical considerations surrounding offering genomic testing at a population level. A within-trial and modelled economic evaluation will be undertaken from an Australian health system perspective to assess the intervention costs and outcomes.

Discussion: This trial will inform the clinical and personal utility of introducing genomic testing into the health system for melanoma prevention and early detection at a population-level.

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1. Introduction

Melanoma is associated with significant morbidity and mortality [1,2]. Despite being a relatively common cancer among European populations [3], > 80% of melanoma diagnoses could be prevented through reduced sun exposure [4] and improved sun protection (i.e. primary prevention behaviors) [5,6]. Secondary prevention through skin examination increases the likelihood of identifying melanoma at an early stage, when disease prognosis is better [6,7]. Preventive behaviors remain sub-optimal for people in high incidence countries such as Australia [7].

A unique strategy for improving melanoma prevention behaviors in the general population is provision of information on personal genomic risk of melanoma. Some common genomic variants have moderate effect sizes for melanoma risk [8,9], and have been shown to be as good as or better than, traditional self-reported risk factors (such as skin type) for predicting melanoma risk [10–13]. Genomic risk information can also make some people aware of their higher melanoma risk due to genetic susceptibility, despite having a low-risk phenotype (e.g. darker skin) [14,15].

Health behavior theories [16–18] indicate that personal genomic risk information, together with education about melanoma prevention and early detection, may be an effective motivator of behavior change. This potential impact is linked to the highly personalized nature of genomic information, mediators of behavior change (e.g. confidence in undertaking preventive behaviors) and to other downstream effects such as conversations about disease risk with family members, friends and health professionals [19].

Previous studies have shown that providing genetic testing results for high-penetrance single-gene variants can motivate preventive behaviors [20,21] and improve risk perception [22] in people who have received a diagnosis and/or have relatives diagnosed with melanoma. However, the generalizability of these findings to the wider population is unclear. Most studies of genomic risk interventions in healthy participants have focused on smoking cessation, diet and physical activity behaviors. Overall, these studies have not demonstrated a significant effect, but they have been limited by small sample sizes and a high risk of bias [23,24].

The *Melanoma Genomics Managing Your Risk* randomized controlled trial builds on our previously reported focus group research [25,26] and pilot study [19,27], both of which suggested that providing personal melanoma genomic risk information to the public was feasible and acceptable, with some preliminary indication of improved preventive behaviors and no evidence of adverse psychological effects. In this trial, we will evaluate the efficacy and cost-effectiveness of providing personal genomic risk information as a potential melanoma prevention strategy. We hypothesize that providing personalized information on genomic risk of melanoma to the general population will motivate reduced exposure to UV overall, and that the effect may differ according to traditional risk (including phenotypic risk factors, such as moles and hair color, as well as other risk factors such as family history). We are also examining the broader social, psychological, and ethical implications associated with this type of personalized genomic information [28], as we are aware of the importance of exploring unintended consequences of new health interventions [29]. This study will help us to understand the personal utility (individuals' perceptions and expectations of genomic testing and the ways they react to and use this information in their daily life) [30] and clinical utility (the effect on health outcomes such as the prevention of skin cancer, morbidity, mortality) [31] of providing genomics-based risk information to the general population. If appropriate, our findings will guide research translation and implementation to optimize public health [32,33].

2. Aims

The primary aim of this randomized controlled trial is to evaluate the efficacy of providing information on personal genomic risk of melanoma in reducing UV exposure at 12 months. We will examine UV exposure according to low and high traditional risk groups in the intervention and control arms.

The secondary aims are to evaluate:

(i) the intervention's effect on time-specific UV exposure and self-reported UV exposure, sun protection behaviors, and skin examinations at 12 months;
(ii) the effect on other behavioral outcomes including tanning, sunburn frequency and hypothesized mediators of behavior change;
(iii) psychological outcomes, including skin cancer-related worry and distress;
(iv) the intervention's effect on short-term outcomes at 1 month;
(v) the impact of personal genomic risk level (low, average, high) on outcomes in the intervention arm;
(vi) ethical considerations surrounding offering genomic testing at a population level;
(vii) social issues arising from the study processes that may affect wider implementation; and,
(viii) cost-effectiveness of the intervention at 12-months and longer-term from an Australian health-system perspective.

3. Methods

3.1. Trial design

The *Managing Your Risk Study* is a two-arm, parallel group randomized controlled trial. The study will be coordinated at The University of Sydney, and study participants will be recruited Australia-wide. This study is funded through a National Health and Medical Research Council (NHMRC) project grant (APP1129822), and has been endorsed by the Australian and New Zealand Melanoma Trials Group (ANZMTG 03.17). Ethical approval has been obtained from the Human Research Ethics Committee at The University of Sydney (2017/163) and this study is prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617000691347). This trial protocol has been prepared according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [34].

3.2. Eligibility criteria

Eligible participants will meet all of the following criteria:

1. Aged 18–69 years at the time of recruitment. The upper restriction is intended to maximize the impact of the intervention, which aims to prevent future melanoma and other skin cancers. People > 70 years are also more likely to have co-morbidities that may influence their time outdoors.
2. Never had a melanoma, since a previous diagnosis is likely to influence the behaviors under study in the trial.
3. Part or full European ancestry. Current knowledge of genomic risk for melanoma is based almost entirely on populations of European origin, and therefore the genomic risk estimates may be less