A Systematic Review on the Impact of Genetic Testing for Familial Melanoma II: Psychosocial Outcomes and Attitudes

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Keywords

Melanoma · Genetic testing · Psychosocial impact

Abstract

Background: Although genetic testing for known familial melanoma genes is commercially available, clinical implementation has been restrained as utility is unclear, concerns of causing psychological distress are often cited, and consumer interest and perceptions are not well understood. A review of studies exploring participant-reported psychosocial outcomes and attitudes towards genetic testing for familial melanoma will provide insight into common emotional and cognitive responses. **Methods:** Database searches of PubMed, Embase, CINAHL, PsycINFO and the Cochrane Library were conducted using a date range of January 1995 to June 2020. Studies examining any psychosocial outcomes alongside genetic testing (real or hypothetical), in participants described as having a high risk of melanoma, were eligible. A narrative synthesis of results was used to describe psychosocial outcomes and summarise participant beliefs and attitudes towards genetic testing. **Results:** Limited evidence of adverse psychosocial outcomes was found. No impacts on perceived risk or control were reported, and mini-

mal decisional regret was recorded. Generalised distress was comparable between both genetic mutation carriers and non-carriers, often decreasing over time from pretesting levels. Melanoma-specific distress was frequently higher in carriers than non-carriers; however, this difference was present prior to testing and often associated with personal melanoma history. Overall, participants' attitudes towards testing were largely positive, with benefits more frequently described than limitations, and support for testing minors was strong. **Conclusions:** This review has found evidence of few adverse psychological outcomes following genetic testing. There was no indication of increased distress after genetic test results had been disclosed. If these findings were replicated in additional, larger, diverse populations over a longer follow-up period, this would be compelling evidence to guide clinical recommendations.

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Introduction

It is estimated that 1% of primary melanoma cases occur within families with a very strong history of melanoma [1]. To date, approximately 10 high-penetrance genes

conferring a significantly increased risk of melanoma have been identified; however, they explain only around 22% of the familial melanoma cases [2]. By far the most common causative gene for familial melanoma is *CDKN2A*, a gene implicated in cell cycle regulation [3]. Pathogenic variants in *CDKN2A* incur a 52% lifetime risk of melanoma and an increased risk of pancreatic cancer [4]. The penetrance of *CDKN2A* for pancreatic cancer risk is not as well established, with European and North American studies estimating an 18% lifetime risk [5, 6], while Australian cohort studies have found no evidence of increased risk [6]. Possible explanations for the discrepancy may be due to lower smoking rates in Australia and/or differing *CDKN2A* mutations in Australian populations [6].

Although genetic testing using a panel of known susceptibility genes is commercially available [7], clinical implementation has been restrained as utility in improving prevention is unclear [8]. Additionally, there are concerns about causing psychological distress [9], and a number of complex ethical and public health issues are debated [10]. Previous systematic reviews on predictive genetic testing for various diseases have reported limited evidence of adverse psychosocial impact [11–13], and a modest impact on increasing preventative behaviour [14–16]. There have been no previous systematic reviews focusing solely on outcomes relevant to genetic testing for familial melanoma. This is the second in a 2-part systematic review series, where the first reported impact on preventative behaviour (see part I, the other paper of this series, DOI: 10.1159/000513919), while this review focuses specifically on psychosocial outcomes. This review explores a range of complex psychosocial outcomes beyond psychological distress, including attitudes towards genetic testing and testing of minors, as well as factors influencing uptake.

Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [17] and was preregistered with PROSPERO (International Prospective Register of Systematic Reviews), and it can be accessed here: https://www.crd.york.ac.uk/prospere/display_record.asp?ID=CRD42020186881.

Inclusion criteria comprised any studies where (i) participants were perceived to be at high-risk of developing melanoma, (ii) genetic testing (or hypothetical scenarios) was offered, and (iii) psychosocial outcomes were available. Only original research published in English was assessed for eligibility. The following databases were searched: Pubmed, Embase, CINAHL, PsycINFO and

Table 1. Glossary of commonly used terms

Carrier/ non-carrier	A person who tests positive or negative for a familial pathogenic variant (in <i>CDKN2A</i>)
Affected/ unaffected	A person with or without a personal history (of melanoma)
Controls	Participants who received counselling without genetic testing

the Cochrane Library using terms related to genetic testing, psychosocial impact and melanoma risk; search strings are provided in online supplementary Table S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000513576). A date range of January 1995 (discovery of *CDKN2A* as a melanoma gene) until June 2020 was applied. Screening was performed by reviewing titles/abstracts. Eligibility was assessed by reviewing full text. A subsequent backwards and forwards citation search was completed. The QualSyst assessment tool [18] was used to review the quality of studies included in the review. Screening, eligibility, quality and risk assessment was performed by author C.P., and a second author (T.Y.) screened 10% of the records and assessed quality in 25%. Data were extracted using a standardised report form, collecting: citation, study design, study population, outcomes and follow-up time points. Narrative synthesis was used to describe results, as the differences in methods and outcomes measured prevented result pooling [19].

A glossary of commonly used terms throughout this review is provided in Table 1.

Results

In total, 2,352 articles were identified in the database and citation search, and 1,697 remained after removing duplicates. A further 1,590 articles were removed after screening titles/abstracts, leaving 49 articles assessed for eligibility by full-text review (Fig. 1). Thirty articles were excluded for reasons described in Figure 1. The final review included 21 articles describing outcomes from 12 unique studies, which included a total of 1,137 study participants. Two studies used hypothetical scenarios to explore psychosocial responses, and the remaining studies used *CDKN2A* genetic testing to provide genetic risk assessment. No other familial melanoma risk genes were assessed. The follow-up period ranged from cohort studies to 2 years after test result disclosure. Table 2 describes characteristics of studies, including outcomes assessed. Interrater reliability scored highly between authors for screening and quality assessment, producing a kappa score of 0.88 for screening and 0.91 for quality assess-

Fig. 1. Flowchart of the database and citation search.

ment. Quality assessment found all studies rated moderate to high in quality (online suppl. Table S2).

Adverse Psychological Outcomes

The most commonly reported psychological outcomes assessed included: generalised anxiety and depression [20–26]; melanoma-specific distress [20–28]; cancer (melanoma and pancreatic) worry/concern [24, 26–28]; and decision (for genetic testing) regret [20, 24–26]. Most studies utilised validated, widely accepted surveys such as the Hospital Anxiety and Depression Scale which includes two 7-item subscales to measure both anxiety and depression, and is widely used in research

[29]; the Impact of Events Scale, which comprises 15 items to assess intrusive and avoidant cognitions and behaviours in respondents and has been used to measure disease-specific distress [30]; and the Multidimensional Impact of Cancer Risk Assessment scale, a 25-item survey that is commonly used to assess distress and uncertainty in people undergoing genetic testing [31]. Other validated questionnaires were used to capture cancer worry [32–34], decision regret [35], mental health [36], anxiety and depression in adolescents [37, 38], and lastly open-ended and semi-structured interviews were used in 3 studies [25, 26, 28].

Table 2. Study characteristics of articles included in this review

Reference	Population	Participant status	Study design	Outcomes assessed	Summary of major findings
Riedijk et al. [39], 2005 ^a	<i>n</i> = 66, Netherlands (52% male)	Decliners of genetic testing <i>n</i> = 66	Cross-sectional, survey of test decliners	Generalised distress, uptake (reasons for declining)	Increased anxiety was associated with test-declining reasons for declining testing reported
Kasparian et al. [28], 2006 ^b	<i>n</i> = 40, Australia (52% male)	DX+FH+ <i>n</i> = 10, DX+FH- <i>n</i> = 10, DX-FH+ <i>n</i> = 10, DX-FH- <i>n</i> = 10	Cross-sectional, qualitative, hypothetical	Disease-specific distress	Those with personal/family history of melanoma were more likely to anticipate calmly accepting high-risk feedback, compared to those with no melanoma history, who anticipated feeling increased distress
Kasparian et al. [47], 2007 ^b	<i>n</i> = 40, Australia (52% male)	DX+FH+ <i>n</i> = 10, DX+FH- <i>n</i> = 10, DX-FH+ <i>n</i> = 10, DX-FH- <i>n</i> = 10	Cross-sectional, qualitative, hypothetical	Uptake, attitudes on testing minors, benefits and limitations of testing	Intended uptake was associated with empiric risk of melanoma. Half of the participants supported testing availability for minors, another third were supportive when medically recommended. Nominated benefits of testing outweighed limitations
de Snoo et al. [22], 2008 ^b	<i>n</i> = 94, Netherlands (50% male)	Received genetic testing <i>n</i> = 75, declined genetic testing <i>n</i> = 19	Cross-sectional, pretesting survey	Uptake, generalised distress, disease-specific distress	Both acceptors and decliners of testing had low generalised distress and melanoma-specific distress, with no significant difference reported between groups Reasons for accepting/declining testing reported
Kasparian et al. [23], 2008 ^a	<i>n</i> = 121, Australia (50% male)	Family members of CDKN2A+ individuals (DX+ <i>n</i> = 37, DX- <i>n</i> = 84)	Cross-sectional, pretesting survey	Generalised distress, disease-specific distress, perceived risk	All levels of distress measured were relatively low Personal history of melanoma was associated with significantly greater melanoma-specific distress, however comparable generalised distress to unaffected participants Perceived risk was significantly associated with personal history of melanoma
Kasparian et al. [20], 2009 ^a	<i>n</i> = 119, Australia (48% male)	Declined testing <i>n</i> = 76, attended counselling and declined testing <i>n</i> = 4, not offered testing <i>n</i> = 14, CDKN2A+ <i>n</i> = 15, CDKN2A- <i>n</i> = 5, CDKN2A test inconclusive <i>n</i> = 5	Longitudinal (before disclosure, 2 weeks, 1 year)	Uptake, generalised distress, disease-specific distress, decision regret, perceived risk	Both carriers and test decliners reported significantly reduced generalised distress from baseline levels, over time Melanoma-specific distress remained stable over time, for both carriers and test decliners No significant differences in generalised or specific distress between carriers and test decliners, at any time point 67% intended to pursue testing at baseline; however, actual uptake was 21% Perceived risk remained relatively stable over time
Bergemar et al. [40], 2009	<i>n</i> = 11, Sweden (55% male)	DX- CDKN2A+ <i>n</i> = 4, DX- CDKN2A- <i>n</i> = 5, DX- CDKN2A test inconclusive <i>n</i> = 2	Longitudinal (before disclosure, immediately after disclosure, 6 months, 1 year)	Generalised distress, perceived risk, benefits and limitations of testing	Generalised distress decreased over time; however, sample size does not allow statistical analysis Perceived risk remained relatively stable over time. Carriers appeared to underestimate risk, while non-carriers often overestimated their risk
Leaf et al. [46], 2010 [*]	<i>n</i> = 25, USA (48% male)	CDKN2A+ <i>n</i> = 12, CDKN2A- <i>n</i> = 13	Cohort within larger parent study, longitudinal (before disclosure, 1 year)	Perceived control	Greater perceived control was associated with belief in personal responsibility for health Belief that cancer is "God's will" was not associated with level of perceived control (over future melanomas)
Taber et al. [49], 2010 [*]	<i>n</i> = 61, USA (51% male)	DX+ CDKN2A+ <i>n</i> = 19, DX- CDKN2A+ <i>n</i> = 15, DX- CDKN2A- <i>n</i> = 27	Longitudinal (before disclosure, immediately after counselling, 2 years)	Attitudes towards testing minors	87% of adults, who received genetic testing, were supportive of testing availability to minors; 83% of carriers wanted testing for their own children
Christensen et al. [21], 2011	<i>n</i> = 19, USA (47% male)	DX+ <i>n</i> = 19, CDKN2A+ <i>n</i> = 3, CDKN2A- <i>n</i> = 16	Longitudinal (before disclosure, 3 months)	Uptake, generalised distress, disease-specific distress, benefits and limitations of testing	No changes in generalised or specific distress over time Participant reported benefits and limitations of testing provided 70% of those contacted proceeded with genetic testing
Bränström et al. [41], 2012	<i>n</i> = 312, international (39% male)	Previously received genetic testing <i>n</i> = 66, CDKN2A+ <i>n</i> = 37, CDKN2A- <i>n</i> = 29	Cross-sectional, international questionnaire, hypothetical scenarios	Perceived risk, benefits and limitations of testing	79% of participants perceived their risk as higher than the general population (all participants from families with multiple melanomas) Highest rated benefit of testing was "information on children's risk," followed by "assisting research" and "understanding own risk"
Aspinwall et al. [24], 2013 [*]	<i>n</i> = 61, USA (54% male)	DX+ CDKN2A+ <i>n</i> = 19, DX- CDKN2A+ <i>n</i> = 15, DX- CDKN2A- <i>n</i> = 27	Longitudinal (before disclosure, immediately after disclosure, 1 month, 6 months, 1 year, 2 years)	Generalised distress, disease-specific distress, decision regret, benefits and limitations of testing	For carriers and non-carriers, generalised distress decreased significantly over time, from predisclosure levels Melanoma-specific distress higher in participants with previous melanoma diagnosis, and relatively stable over time; 3 major categories of benefits identified: emotional benefits (relief), informational benefits (understanding of risk) and behaviour benefits (motivation for prevention)

Table 2 (continued)

Reference	Population	Participant status	Study design	Outcomes assessed	Summary of major findings
Glanz et al. [42], 2013	<i>n</i> = 73, USA (31.5% male)	Intervention group <i>n</i> = 35 (CDKN2A+ <i>n</i> = 3), control group <i>n</i> = 38	RCT, longitudinal (before disclosure, 4 months)	Perceived risk	No change in perceived risk from baseline to 4 months after disclosure, for either intervention or control group
Aspinwall et al. [58], 2014*	<i>n</i> = 59, USA (54% male)	DX+ CDKN2A+ <i>n</i> = 18, DX- CDKN2A+ <i>n</i> = 14, DX- CDKN2A- <i>n</i> = 27	Longitudinal (before disclosure, immediately after disclosure, 1 month, 6 months, 1 year, 2 years)	Perceived risk	No sustained changes from baseline perceived risk for either group Unaffected carriers consistently underestimate their risk Non-carriers decreased their perceived risk after test disclosure (to a more accurate perception); however, perceived risk increased to overestimate risk at later time points Affected carriers' risk perception was fairly accurate and stable over time
Aspinwall et al. [45], 2015*	<i>n</i> = 59, USA (54% male)	DX+ CDKN2A+ <i>n</i> = 18, DX- CDKN2A+ <i>n</i> = 14, DX- CDKN2A- <i>n</i> = 27	Longitudinal (before disclosure, immediately after disclosure, 1 month, 6 months, 1 year, 2 years)	Perceived control	45% of participants increased their perceived control from pretesting measures, while 38% reported no change, and 17% decreased their perception of control At the group level, non-carriers increased perceived control The majority of decreased perceived control was detected in carriers; however, decrease was relatively small (1.1 points on a 5-point scale)
Taber et al. [44], 2015*	<i>n</i> = 96, USA (52% male)	Testing for familial mutations, CDKN2A+ <i>n</i> = 17, CDKN2A- <i>n</i> = 38, FH+ control group (no testing) <i>n</i> = 31	Longitudinal, controlled (before disclosure, immediately after disclosure, 1 month)	Perceived risk (understanding and acceptance of risk information)	Participants who received genetic testing reported greater understanding and acceptance of risk information compared to the control group which received equivalent counselling without genetic testing
Levin et al. [48], 2017	<i>n</i> = 128, Norway	CDKN2A+ <i>n</i> = 56, CDKN2A- <i>n</i> = 70, declined testing <i>n</i> = 2	Cross-sectional (after disclosure)	Uptake	66% of those contacted proceeded with genetic counselling 98% of those who received counselling proceeded with genetic testing
Aspinwall et al. [50], 2018*	<i>n</i> = 114, USA (52% male)	Testing for familial mutations, CDKN2A+ <i>n</i> = 28, CDKN2A- FH+ <i>n</i> = 41, FH+ control group (no testing) <i>n</i> = 45	Longitudinal, controlled (1 month, 1 year)	Benefits and limitations of testing	At 1-month and 1-year post-test disclosure time points, both carriers and non-carriers felt more informed and prepared to manage risk, compared to no-test control group Non-carriers reported significantly more relief than carriers and no-test controls Carriers and no-test controls reported more negative emotions in response to their risk
Stump et al. [26], 2018	<i>n</i> = 18 (minors), USA (56% male)	CDKN2A+ <i>n</i> = 9, CDKN2A- <i>n</i> = 9	Longitudinal (before disclosure, 1 week, 1 month, 1 year)	Generalised distress, decision regret, attitudes on testing minors	Generalised anxiety and depression measured low at all time points, with no differences between carriers and non-carriers Generalised depression decreased from baseline level, over time No decision regret reported from parents who consented testing for their children Parent's opinion on age in which testing should be available was a mode of 12 years of age
Zhu et al. [25], 2018 [§]	<i>n</i> = 63, USA (34% male)	CDKN2A+ <i>n</i> = 15, FH+ CDKN2A- <i>n</i> = 40, spouses <i>n</i> = 8	Longitudinal (before disclosure, immediately after disclosure, 6 months)	Generalised distress, disease-specific distress	No reported change in generalised distress over time for either carriers or non-carriers Disease-specific distress was significantly higher in carriers at 6 months after testing (not measured at other time points) Carriers reported feeling "sadness" significantly more than non-carriers at all time points
Leof et al. [27], 2019 [§]	<i>n</i> = 63, USA (34% male)	CDKN2A+ <i>n</i> = 15, FH+ CDKN2A- <i>n</i> = 40, spouses <i>n</i> = 8	Longitudinal (before disclosure, immediately after disclosure, 6 months)	Disease-specific distress, perceived risk	Carriers reported significantly more pancreatic cancer-specific and melanoma-specific distress, both before disclosure and at 6 months of follow-up Melanoma-specific distress in unaffected carriers was not significantly different from that of non-carriers at 6 months of follow-up Carriers perceived themselves at increased risk over non-carriers, both before and after test disclosure

Superscripts [§], [#], [^], ^{*}, and [§] indicate records which are reporting from the same study. DX, personal history of melanoma; FH, family history of melanoma; CDKN2A+/-, carrier/non-carrier of CDKN2A mutation; RCT, randomized controlled trial.

Generalised Distress (Anxiety and Depression)

Generalised distress was reported in 9 publications from 7 separate studies [20–26, 39, 40]. All studies used validated measures to quantitatively assess outcomes related to generalised anxiety and depression [20–26, 39, 40]. Within studies, results were compared between a variety of subgroup populations, such as mutation carriers, non-carriers, test acceptors, test decliners, those previously diagnosed with melanoma (affected) and those without (unaffected). Across all studies, mean distress scores were low and below clinically relevant thresholds. No studies reported an increase from baseline measures in generalised anxiety or depression following test disclosure. Four studies reported no significant change in anxiety in carriers or non-carriers over time [21, 25, 26, 40]. One study ($n = 119$) reported no association between generalised distress scores at baseline (before testing) and personal melanoma history [23]. At 12 months after testing, this study measured a significant decrease in anxiety for both acceptors and decliners of testing [20]. Another study ($n = 60$), which compared affected carriers, unaffected carriers and non-carriers, found a significant decrease in anxiety across all groups over time [24]. One cross-sectional study which surveyed participants prior to testing reported low levels of anxiety and depression for both acceptors and decliners of testing; however, anxiety was slightly higher in decliners (mean anxiety score 2.5; SD 2.8) compared to acceptors (mean anxiety score 1.7; SD 1.9) [22, 39]. Two studies reported significant decreases in depression over time, which was not dependent on carrier status [20, 26]. One study found carriers reported “sadness” levels significantly greater than non-carriers; however, this difference was existing at baseline and remained unchanged at 6 months of follow-up [25].

Disease-Specific Distress and Worry

Disease-specific distress or worry for melanoma was reported in 8 studies [20–28] and for pancreatic cancer in 3 studies [22, 24, 27].

Overall, melanoma-specific distress was relatively low and stable over time, with no significant changes from before to after genetic testing [20, 21, 24]. Group comparisons in one study found no significant differences in baseline distress between acceptors and decliners of testing [22]. Another study reported no differences in melanoma-specific distress between carriers, test acceptors or test decliners at either baseline or 12 months of follow-up [20]. Three studies reported significantly higher distress in specific subgroups including: affected participants [23], affected carriers [24] and in carriers (both affected

and unaffected) [25], with no significant change in distress from pre- to post-testing surveys.

Four studies reported on melanoma-specific worry [24, 26–28]. A study evaluating responses to hypothetical scenarios found that a personal or family history of melanoma was associated with calmly accepting increased-risk results [28]. In comparison, those without any melanoma history anticipated feeling increasingly worried, scared and/or shocked [28]. Two later studies, which provided genetic testing, also considered personal history and reported that affected carriers had significantly greater worry than unaffected carriers and non-carriers, with no significant change over time [24, 27]. A study, which tested 18 minors, reported a significant decrease in melanoma-related worry over time (1 year), for both carriers and non-carriers, with no significant difference between groups [26].

Three studies assessed impact of genetic testing on pancreatic cancer-specific worry. One study reported that approximately half of the participants were both surprised and anxious to learn about pancreatic cancer risk [22]. Another study found that carriers had significantly greater pancreatic cancer worry at both baseline (before testing) and 6 months after disclosure [27]. Similarly, another study found both carriers and those with a pancreatic cancer family history recorded significantly greater worry [24]. Furthermore, mean pancreatic cancer worry scores for all participants increased slightly at 1 month, then decreased significantly from 6 months to 2 years after test disclosure [24].

Perceived Risk and Control

Ten publications, from 7 unique studies, reported outcomes on participants’ perceived risk of melanoma [20, 23, 27, 40–44] and perceived control of subsequent melanomas [45, 46]. Four longitudinal studies found no sustained significant changes in perceived risk from pre- and post-testing, with follow-up ranging from 4 months to 2 years [27, 40, 42, 43]. Carriers and those with a personal history of melanoma reported higher perceived risk compared to non-carriers and unaffected individuals [23, 27, 41, 43]. A study comparing acceptors and decliners of testing found no significant baseline differences in reported risk perception [23]. When comparing objective risk to perceived risk, one study revealed that on average, carriers underestimated risk, while non-carriers overestimated their risk [40]. Likewise, Aspinwall et al. [43] found that unaffected carriers consistently underestimated their risk, non-carriers overestimated, while affected carriers were more accurate. Furthermore, Aspinwall et al. [43]

reported that while non-carriers recorded decreased perceived risk immediately after test disclosure, long-term follow-up from 1 month to 2 years found levels returning to previous levels of overestimated risk perceptions. Lastly, one study reported that understanding and acceptance of risk information was higher in those who received genetic testing, compared to those who received equivalent counselling without genetic testing [44].

Two studies reported on perceived control of developing subsequent primary melanoma(s) [45, 46]. In one study, 45% of participants reported increased perceived control 2 years after genetic testing, while 38% reported no change, and 17% reported decreased perception of control [45]. In the second study, individuals who reported greater personal responsibility over their health were also found to have higher perceived control over melanoma risk [46], while religiosity, including belief that cancer was “God’s will,” was not associated with perceived control [46].

Decisional Regret

Minimal decisional regret over uptake of genetic testing was reported in 4 studies [20, 24–26]. Using the Decision Regret Scale, Kasparian et al. [20] reported minimal regret among carriers and non-carriers. Out of a possible score of 100, with higher scores representing great regret, the mean score for carriers was 15, compared to 6 for non-carriers [20]. A study offering testing for minors surveyed participants’ mothers with open-ended questions and found no self-reported regret in consenting to testing for their children [26].

Uptake of Genetic Testing

An early Australian study, using hypothetical testing scenarios, reported 68% of participants would seek genetic testing should it become available [47]. Intentions to take up testing was greater in participants with higher empiric risk. For example, 90% of participants with both family and personal history of melanoma would pursue testing if available, compared to 30% of participants with no melanoma history [47]. Additionally, the study used hypothetical testing scenarios of different *CDKN2A* penetrance models (100, 90, 30%) and found little difference in uptake between 100 and 90%; however, uptake declined significantly in the 30% penetrance scenario [47].

Four studies reported the percentage of contacted participants who proceeded with genetic testing, which included 21 [20], 66 [48], 70 [21] and 77% [22]. Kasparian et al. [20] reported that intentions to have genetic testing at baseline were 67%. However, at the conclusion of the

study only 21% of participants had undergone genetic testing [20]. The low uptake of testing was attributed to study design factors including participants required to approach a clinical genetic service themselves to request testing and needing to meet the clinics criteria for publicly funded genetic testing [20].

Two studies reported participants’ reasons for declining testing, which included: “happy with life how it is,” “not relevant to me” and “can’t tell me if I’ll definitely get melanoma” [20, 39]. Factors positively associated with uptake included: female gender, family history, older age, having children, perceived risk, higher empiric pretest risk, lower pretest anxiety and the gene penetrance [20, 22, 39, 47, 48].

Attitudes on Testing Minors

Three studies reported outcomes on participants’ attitudes towards testing minors [26, 47, 49]. When asked about attitudes towards testing minors for familial melanoma, approximately half of the participants (53%) were supportive generally, a third stipulated only under medical recommendation, and 10% opposed melanoma genetic testing in minors [47]. A later, quantitative study of adults who received testing for *CDKN2A* found 87% expressed support for testing availability for children, with greater support in individuals diagnosed with melanoma at a younger age [49]. Participants’ perceived benefits for testing children included raising risk awareness and improving primary and secondary prevention [26, 49]. The perceived minimum testing age ranged from 0 to 25 years, with 12 being the most common answer [49]. A study which provided genetic testing for 18 minors (mean age of 12.4 years), interviewed parents of participants 1 month and 1 year after testing, and found all mothers rated the experience beneficial, due to promoting risk awareness (90%) and increasing sun protection behaviour (82%) [26].

Perceived Benefits and Limitations of Genetic Testing

Seven studies provided participant-reported outcomes on potential benefits and limitations of genetic testing for familial melanoma [20, 21, 24, 40, 41, 47, 50], 2 of which used only hypothetical scenarios of testing [41, 47]. Overall, benefits were far more frequently reported than limitations, for example, in one study using open-ended questions, nearly 95% of participants provided at least one benefit at each assessment, compared to 16% of all study participants who provided a perceived limitation of testing [24]. Across the studies, the most commonly cited benefits reported included: increased awareness/certainty

of own risk, learn about children's risk, motivation for sun-protective behaviour and screening, assisting research and relief for non-carriers. The most commonly identified disadvantages included: negative psychosocial reaction, concern about effect on family, possible test inaccuracy, reduced protective behaviour (for non-carriers) and insurance discrimination. Furthermore, 3 studies reported results separately for carriers and non-carriers [24, 40, 50]. Carriers most commonly rated motivational benefits (e.g., for sun protection), while non-carriers rated emotional relief regarding personal and children's risk as most important. Both carriers and non-carriers frequently reported informational benefits. Predictably, increased worry for personal risk and children's risk were often reported by carriers as disadvantages of testing.

Discussion

Based on our systematic review there is limited evidence that genetic testing for familial melanoma causes significant psychological distress. The evidence across the studies, which are based on well-validated multi-item inventories, indicates that generalised distress does not appear to be impacted by testing outcomes, carrier status or personal history. Although measures of psychological distress across the studies were, on average, relatively low and below clinically relevant thresholds, significant differences were detected between subgroups. Presence of higher pretest anxiety in some studies suggests that the testing process itself may cause a short-term increase in generalised distress, which resolves quickly thereafter. In comparison, disease-specific distress seems associated with carrier status and/or personal history. Quantitative measures show that carriers and those with personal history, on average, report significantly higher levels of disease-specific distress, with little change over time. Elevated disease-specific distress in these groups is present at baseline, prior to testing, and therefore not the result of testing outcomes and possibly due to personal or family history. Incidence of higher disease-specific distress in carriers and those previously diagnosed with melanoma is expected and is potentially important in motivating risk-reducing behaviour. Common psychological constructs predict that while excessive levels of distress may have a detrimental impact on health behaviour uptake, moderate levels of distress promote risk reduction [51].

Somewhat surprisingly, there was no evidence that genetic risk assessment had any impact on participants' perceived risk of subsequent melanomas. While it would ap-

pear illogical that personalised genetic risk feedback would not influence perceived risk, it is however consistent with other multifactorial diseases [16]. One reasoning for unchanging risk perception would be if pre-existing beliefs were accurate. On closer examination, it appears while carriers with a previous melanoma diagnosis held fairly accurate risk perceptions, unaffected carriers more often underestimated their risk. When applied to psychological models on health behaviour such as the Protective Motivation Theory [52], this lack of impact on perceived risk may translate to a lack of adapting risk-reducing behaviours. It is important to consider the possible differences in how genetic risk results are disclosed, and how much risk education is provided. This is often not described in detail in studies, and therefore, conclusions on efficacy cannot be drawn. However, future investigation into genetic risk counselling and education methods may be beneficial [53].

When reviewing participants' attitudes and beliefs regarding wider availability of genetic testing for familial melanoma, feedback was largely positive, and participants were also in favour of making testing available to minors. The most frequently nominated benefits included greater awareness of own risk and children's potential risk, and motivation for protective behaviour and screening. For those testing negative for a familial mutation, relief rated highly. Concerns regarding impact on relatives and insurance discrimination were also voiced. Both topics are complex issues and require meaningful discussion in pretest counselling, allowing an informed decision to proceed with testing [53]. Positively, several countries have introduced policies or legislation to protect against the use of genetic test information in medical and/or life insurance underwriting [54].

Measured uptake of genetic testing in research provides some indication of the potential demand from the familial melanoma cohort, if testing became more widely available. It is encouraging to see evidence that intentions to pursue genetic testing appear mostly aligned with empiric risk [47]. This may ease concerns that testing services may be overwhelmed by individuals deemed ineligible for testing. One study reported a much lower test uptake (21%) [20] than others. Initially, this appears to be an outlier; however, it may actually represent a more realistic model of uptake. In this study, participants were required to arrange testing themselves thereby reflecting real-life practice, compared to other study designs which followed more streamlined protocols. This is consistent with uptake of *BRCA1* and *BRCA2* testing, which was higher when offered to a highly invested research popula-

tion (78%) [55], as compared to clinical cohorts of 30% in men and 62% in women [56]. The opportunity to learn more about children's potential risk also rated highly as a motivator for uptake of genetic testing [22]. Reasons for declining testing included those relating to convenience, such as time and travel, and the sentiment "I'm happy with life how it is" [20]. A study from the Netherlands reported an association with generalised anxiety and disease-specific worry with declining genetic testing [22, 39]; however when measured in an Australian cohort, no difference in distress was reported between test acceptors and decliners [20].

There are limitations to consider for this systematic review. The heterogeneity of study methodology used and the inclusion of hypothetical scenarios to draw participant responses places difficulty in synthesising outcomes and limits subsequent conclusions. However, it was assuring to note that outcomes provided in the hypothetical studies were closely aligned with clinical study outcomes reviewed. Further limitations to generalisability include small, homogenous (white, well-educated) self-selected study populations who were highly motivated to participate in the study, and in some studies included several participants from a small number of families. It would be interesting to see whether studies offering genetic testing to a large number of unrelated individuals from differing socio-economic backgrounds yield similar psychosocial outcomes. The overall low sample sizes and lack of gold standard randomised controlled trials place restrictions on the strength of evidence drawn from this review [57]; however, the low incidence of mutation carriers and ethical issues of controlled randomisation are limiting. Therefore, as this is an emerging field with limited research conducted, the importance of capturing all available outcomes was prioritised, and subsequent conclusions are made with caution. While 5 studies followed participants for 1–2 years, a third of the studies in this review were cross-sectional, and another 3 included a follow-up period of 6 months or less, which limits conclusions regarding the long-term psychosocial consequences of genetic testing in familial melanoma. Lastly, grey literature and conference abstracts were not included in the search strategy, and therefore a publication bias risk exists.

Conclusions

This systematic review has found limited evidence of adverse psychological impacts of genetic testing or negative effects on risk perception. Study participants' atti-

tudes towards and perceptions of genetic testing were positive, with perceived benefits far outweighing perceived disadvantages. If larger studies, with more heterogeneous populations and long-term follow-ups produced comparably positive findings, this would be invaluable in informing future clinical practice.

Key Message

Evidence suggests that genetic testing for familial melanoma does not result in adverse psychosocial outcomes.

Statement of Ethics

This is a literature review which did not involve human subject recruitment. Thus, ethical approval was not required.

Conflict of Interest Statement

H.P.S. is a shareholder of MoleMap NZ Limited and e-derm consult GmbH, and undertakes regular teledermatological reporting for both companies. H.P.S. is a medical consultant for Canfield Scientific Inc., Revenio Research Oy and also a medical advisor for First Derm.

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Author Contributions

C.A.P. performed database search, screening, eligibility and quality assessment. T.Y. independently screened 10% of articles and assessed quality of 25% of articles. C.A.P. prepared the first draft of the manuscript. All co-authors contributed to writing, provided intellectual input and approved the final version of the paper.

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