The cost-effectiveness of skin surveillance through a specialised clinic for patients at high risk of melanoma, compared with standard care.

by

Caroline Watts

A thesis submitted in fulfilment of requirements for the degree of Doctor of Philosophy

Sydney School of Public Health, Sydney Medical School

The University of Sydney

May 2016
Dedication

I dedicate this thesis to my parents Ian and Dorothy who instilled in me the values of perseverance and optimism.
Acknowledgements

I feel very fortunate to have had the opportunity to undertake this PhD. In 2010, I completed a Certificate IV course offered to staff at the University of Sydney and was told to think about what I wanted to achieve in my career. When I consulted Graham Mann with a list of ideas for projects that might be worthy of a PhD scholarship, little did I realise that one of them would come to fruition.

I must first acknowledge and thank Anne Cust for taking me on as a student and for providing me with the opportunities to learn. Second, I would like to acknowledge Rachael Morton who together with Anne, have been consummate supervisors, providing considerable guidance and encouragement. I couldn’t have achieved this without you! And to Graham Mann and Scott Menzies, thank you for your invaluable advice and encouragement. I would also like to acknowledge Chris Goumas who got me started with SAS and generously answered my basic questions and as I progressed, helped me solve more difficult problems. To those who have provided moral support and assistance with my project along the way; Kylie Vuong, Anne Kricker, Helen Schmid, Leo Raudonikis, Ritta Kourry and Sharon Lorger; thank you.

Last, but not least I would like to thank my family. Stephen especially, who has been there for me and whose love and support has kept me going. Also thank you to my daughters Pip, Maddie and Imogen for their encouragement. My apologies for the pepper sandwiches you occasionally received for your school lunch. To my siblings Andrew, Sally-Ann and Rosemary; thank you for your support over the years. It has been quite a journey.
Statement of authentication

This thesis is submitted to the University of Sydney in fulfilment of the requirements for the degree of Doctor of Philosophy.

The work presented in this thesis is to the best of my knowledge, my own work except as acknowledged in the text. I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any institution.

Caroline Watts
Table of Contents

Dedication ..................................................................................................................................... 2
Acknowledgements ........................................................................................................................ 3
Statement of authentication ........................................................................................................... 4
Table of Contents .......................................................................................................................... 5
Publications included in this thesis ............................................................................................. 10
Financial support ........................................................................................................................ 13
List of Tables ............................................................................................................................... 14
List of Figures ............................................................................................................................. 16
Abbreviations ............................................................................................................................... 17
Abstract ....................................................................................................................................... 18
Thesis themes and structure ................................................................................................. 20
1 Introduction ............................................................................................................................. 26
  1.1 Melanoma incidence and mortality .............................................................................. 26
  1.2 Risk factors for melanoma ........................................................................................... 27
  1.3 Staging and classification ............................................................................................. 28
  1.4 Keratinocytic cancers incidence ................................................................................... 30
  1.5 Primary and secondary prevention ........................................................................... 31
  1.6 Costs of melanoma and keratinocytic cancers .................................................................... 32
  1.7 The ‘High Risk Clinic’ model ...................................................................................... 33
  1.8 Economic evaluation .................................................................................................... 35
  1.9 Cost-effectiveness analysis ........................................................................................ 37
References ..................................................................................................................................... 39
2 Methods .................................................................................................................................. 45
  2.1 Preamble ....................................................................................................................... 45
  2.2 The Melanoma Patterns of Care study ......................................................................... 45
    2.2.1 Data collection ........................................................................................................ 45
    2.2.2 Selection of a high risk group ............................................................................... 48
  2.3 Micro-costing study ...................................................................................................... 48
  2.4 Cost-effectiveness of the High Risk Clinic .................................................................... 49
    2.4.1 Data linkage ............................................................................................................. 49
    2.4.2 Cost-effectiveness evaluation ............................................................................... 53

5
2.4.3 Quality of life measure ................................................................. 54
2.4.4 Removal of duplicate records ..................................................... 55
2.4.5 Surveillance cost for patients in standard care data set ............. 56
2.4.6 Estimation of the cost of death due to melanoma ....................... 56
2.4.7 Estimation of the cost of death due to causes other than melanoma 56
2.5 References .................................................................................. 57

3 Clinical practice guidelines for identification, screening and follow-up of individuals at high risk of primary cutaneous melanoma: a systematic review ................................................ 58
3.1 Preamble ...................................................................................... 58
3.2 Methods ....................................................................................... 59
  3.2.1 Data sources ............................................................................ 59
  3.2.2 Study selection .......................................................................... 59
  3.2.3 Data extraction .......................................................................... 60
  3.2.4 Quality assessment of the evidence supporting the guideline recommendations 60
3.3 Results ........................................................................................ 60
  3.3.1 Literature search results ............................................................ 60
  3.3.2 Risk factor identification .............................................................. 60
  3.3.3 Definition of high risk groups ....................................................... 60
  3.3.4 Guideline recommendations for screening prior to melanoma diagnosis .......... 65
  3.3.5 Monitoring of naevi .................................................................. 67
  3.3.6 Guideline recommendations for follow-up after a melanoma diagnosis .......... 68
  3.3.7 Guideline recommendations for patient education ....................... 68
  3.3.8 Guideline audience ................................................................... 68
  3.3.9 Quality of evidence supporting the guideline recommendations .......... 68
  3.3.10 Key recommendations ............................................................. 69
3.4 Discussion .................................................................................... 69
3.5 References .................................................................................. 70
3.6 Supplementary Materials ............................................................... 73

4 Characteristics of individuals at higher risk of developing melanoma .......... 91
4.1 Preamble ...................................................................................... 91
4.2 Abstract ....................................................................................... 92
4.3 Introduction .................................................................................. 92
4.4 Materials and Methods ................................................................. 93
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.1</td>
<td>Preamble</td>
<td>132</td>
</tr>
<tr>
<td>6.2</td>
<td>Abstract</td>
<td>133</td>
</tr>
<tr>
<td>6.3</td>
<td>Introduction</td>
<td>134</td>
</tr>
<tr>
<td>6.4</td>
<td>Methods</td>
<td>134</td>
</tr>
<tr>
<td>6.4.1</td>
<td>Study design</td>
<td>134</td>
</tr>
<tr>
<td>6.4.2</td>
<td>Study sample</td>
<td>134</td>
</tr>
<tr>
<td>6.4.3</td>
<td>Micro-costing approach</td>
<td>134</td>
</tr>
<tr>
<td>6.4.4</td>
<td>Direct observation</td>
<td>134</td>
</tr>
<tr>
<td>6.4.5</td>
<td>Review of medical records</td>
<td>135</td>
</tr>
<tr>
<td>6.4.6</td>
<td>Health system costs</td>
<td>135</td>
</tr>
<tr>
<td>6.4.7</td>
<td>Societal costs</td>
<td>135</td>
</tr>
<tr>
<td>6.5</td>
<td>Results</td>
<td>135</td>
</tr>
<tr>
<td>6.5.1</td>
<td>Study population</td>
<td>135</td>
</tr>
<tr>
<td>6.6</td>
<td>Discussion</td>
<td>139</td>
</tr>
<tr>
<td>6.7</td>
<td>Conclusion</td>
<td>140</td>
</tr>
<tr>
<td>6.8</td>
<td>References</td>
<td>141</td>
</tr>
<tr>
<td>6.9</td>
<td>Supplementary materials</td>
<td>142</td>
</tr>
<tr>
<td>7</td>
<td>The cost-effectiveness study of the High Risk Clinic</td>
<td>147</td>
</tr>
<tr>
<td>7.1</td>
<td>Preamble</td>
<td>147</td>
</tr>
<tr>
<td>7.2</td>
<td>Abstract</td>
<td>148</td>
</tr>
<tr>
<td>7.3</td>
<td>Introduction</td>
<td>149</td>
</tr>
<tr>
<td>7.4</td>
<td>Patients and methods</td>
<td>150</td>
</tr>
<tr>
<td>7.4.1</td>
<td>Study population of high risk patients</td>
<td>150</td>
</tr>
<tr>
<td>7.4.2</td>
<td>Surveillance-treatment pathway</td>
<td>151</td>
</tr>
<tr>
<td>7.4.3</td>
<td>Classification and staging of suspicious lesions</td>
<td>152</td>
</tr>
<tr>
<td>7.5</td>
<td>Economic evaluation</td>
<td>153</td>
</tr>
<tr>
<td>7.5.1</td>
<td>Economic methods</td>
<td>153</td>
</tr>
<tr>
<td>7.5.2</td>
<td>Resource use and costs</td>
<td>154</td>
</tr>
<tr>
<td>7.5.3</td>
<td>Model transitions</td>
<td>155</td>
</tr>
<tr>
<td>7.5.4</td>
<td>Quality of life scores and utilities</td>
<td>156</td>
</tr>
<tr>
<td>7.5.5</td>
<td>Sensitivity analyses</td>
<td>156</td>
</tr>
<tr>
<td>7.6</td>
<td>Results</td>
<td>157</td>
</tr>
<tr>
<td>7.6.1</td>
<td>Sensitivity analyses</td>
<td>158</td>
</tr>
<tr>
<td>Section</td>
<td>Title</td>
<td>Page</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>7.7</td>
<td>Discussion</td>
<td>158</td>
</tr>
<tr>
<td>7.8</td>
<td>References</td>
<td>162</td>
</tr>
<tr>
<td>7.9</td>
<td>Tables and figures</td>
<td>166</td>
</tr>
<tr>
<td>7.10</td>
<td>Supplementary materials</td>
<td>175</td>
</tr>
<tr>
<td>8</td>
<td>Discussion and conclusion</td>
<td>191</td>
</tr>
<tr>
<td>8.1</td>
<td>Main findings</td>
<td>191</td>
</tr>
<tr>
<td>8.2</td>
<td>Limitations and strengths</td>
<td>192</td>
</tr>
<tr>
<td>8.3</td>
<td>Other studies</td>
<td>196</td>
</tr>
<tr>
<td>8.4</td>
<td>Implications for policy and practice</td>
<td>197</td>
</tr>
<tr>
<td>8.5</td>
<td>Directions for future research</td>
<td>199</td>
</tr>
<tr>
<td>8.6</td>
<td>Conclusion</td>
<td>201</td>
</tr>
<tr>
<td>8.7</td>
<td>References</td>
<td>202</td>
</tr>
<tr>
<td>9</td>
<td>Appendices</td>
<td>206</td>
</tr>
<tr>
<td>9.1</td>
<td>Questionnaires from Melanoma Patterns of Care study</td>
<td>207</td>
</tr>
<tr>
<td>9.2</td>
<td>National Ethics Application Form application and Protocol</td>
<td>216</td>
</tr>
<tr>
<td>9.3</td>
<td>Ethics approvals</td>
<td>261</td>
</tr>
<tr>
<td>9.4</td>
<td>Review of published health utilities for excisions</td>
<td>274</td>
</tr>
<tr>
<td>9.5</td>
<td>Survey of clinical pathway in standard care</td>
<td>282</td>
</tr>
</tbody>
</table>
Publications included in this thesis

This thesis contains five publications; two published papers and three under review for publication. The research was developed by the candidate with guidance from her four supervisors. The candidate-specific contribution to this thesis, by study, are listed below:


   My roles: Wrote the systematic review protocol, conducted searches and was responsible for the collection and management of the data. Responsible for development of grading system for evidence of recommendations and outcomes evaluation. Responsible for the data analysis and interpretation of results. Responsible for drafting the manuscript and incorporating co-author comments.


   My roles: Responsible for project management, collection of data, data analysis and interpretation of results. Responsible for drafting the manuscript and incorporating co-author comments.


   My roles: Responsible for concept, providing direction for data analysis and interpretation of results. Responsible for drafting the manuscript and incorporating co-author comments.

My roles: Responsible for providing direction for data analysis and interpretation of results.
Responsible for drafting the manuscript and incorporating co-author comments.

5. Watts CG, Cust AE, Menzies SW, Coates E, Mann GJ, Morton RL. The cost-effectiveness of skin surveillance through a specialised clinic for patients at high risk of melanoma, compared with standard care. Submitted to J Clin Oncol. (Chapter 6)

My roles: Writing protocol for data linkage, ethics submission and requested permission to use the 45 and Up study data, data analysis of linked data and High Risk Clinic data, interpretation of results. Responsible for drafting the manuscript and incorporating co-author comments.

Conferences and seminar presentations during candidature


- Watts C, Morton R, Mann G, Menzies S, Cust A The cost-effectiveness of a specialised clinic for individuals at high risk of melanoma. (oral) 11th EADO Congress & 8th World Meeting of Interdisciplinary Melanoma/Skin Cancer Centers, Marseille, France Oct 2015


- Watts C, Morton R, Mann G, Menzies S, Cust A A systematic review of different countries’ clinical practice guidelines for screening and follow-up of individuals at high risk of melanoma. (oral) 8th World Congress of Melanoma, Hamburg, Germany, July 2013

- Watts CG, Cust AE, Mann GJ, Coates E, Menzies SW, Morton RL. Using multiple data sources to determine the cost of managing individuals at high risk of primary melanoma skin cancer in a specialized clinic. (poster) 8th World Congress of Melanoma, Hamburg, Germany, July 2013
- **Watts CG**, Cust AE. Mann GJ, Coates E, Menzies SW, Morton RL. *Using multiple data sources to determine the cost of managing individuals at high risk of primary melanoma skin cancer in a specialized clinic*. (short oral with e-poster) 9th World Congress on Health Economics, Sydney, July 2013


**Dissemination and engagement of research through the media**

- MedicalResearch.com written interview regarding “Specialized Surveillance for Individuals at High Risk for Melanoma: A Cost Analysis of a High-Risk Clinic”. February 2015

**Publications during candidature not included in this thesis**


Financial support

Caroline Watts was supported by a PhD scholarship funded through a Cancer Institute NSW fellowship (#10/ECF/2-06) to Anne Cust, a Cancer Institute NSW Translational Program Grant (10/TPG/1-02) to Graham Mann, and a Sydney Catalyst Top-Up Scholar Award.

Additional conference support

Sydney University Research Student Grant Scheme $1,000
Melanoma Institute Australia travel grant $2,500
List of Tables

Table 1.1 American Joint Committee on Cancer (AJCC) melanoma TMN staging classification for cutaneous melanoma (7th Edition). ................................................................. 29

Table 2.1. List of the International Classification of Diseases for Oncology topography codes for body site of melanoma diagnosis used in the Melanoma Patterns of Care Study .......... 46

Table 2.2 List of the International Classification of Diseases for Oncology morphology codes for melanoma diagnosis used in the Melanoma Patterns of Care Study........................................ 47

Table 2.3 Timeline of applications and permissions for access to the linked dataset .......... 52

Table 3.1. Appraisal of guidelines by country summarising target audience, evidence base for recommendations, screening and follow-up recommendations for high risk high risk individuals.......................................................................................................................... 61

Table 3.2. Risk factors differentiated into ‘high’ and ‘very high risk’ groups in guidelines..... 66

Table 3.3 Summary of guideline recommendations for identification and screening of individuals at high risk of melanoma by order of levels of evidence. ....................................... 69

Table 4.1 Patient and melanoma characteristics for patients at higher risk of developing melanoma compared to lower risk patients ................................................................. 103

Table 4.2. Body site of melanomas according to patients’ sex and risk category ............ 105

Table 4.3. Patient and melanoma characteristics for higher risk patients according to risk factor .................................................................................................................. 106

Table 5.1. Patient and melanoma characteristics for patients at high-risk of developing a new primary melanoma ....................................................................................... 126

Table 5.2. Diagnosis and clinical management of melanoma patients at high-risk compared to those at lower risk of developing a new primary melanoma .................................. 127

Table 5.3. Multivariate prevalence ratios for higher risk patients consulting a specialist rather than a general practitioner as the initial doctor following melanoma diagnosis........ 129

Table 6.1. Characteristics of patients included in the study. ............................................... 136

Table 6.2. Health system costs for patients attending the High Risk Clinic over a 12 month period. .................................................................................................................. 137

Table 6.3. Out of pocket costs for patients attending the High Risk Clinic ..................... 139
Table 6.4. Summary of health system and societal costs AU$ (US$) .........................................139
Table 7.1. Model inputs for High Risk Clinic and Standard care treatment strategies ..........166
Table 7.2. Summary of annual costs in the High Risk Clinic and in standard care ..........168
Table 7.3. Mean total costs (A$) and QALYs per patient over 10 years for each strategy ......171
Table 7.4. Mean excisions per person in High Risk Clinic and standard care from 2006-2010 ...........................................................................................................................................172
List of Figures

**Figure 3.1.** Flowchart for literature search................................................................. 65

**Figure 3.2.** Geographical region as basis for categorisation of risk factors........... 65

**Figure 5.1.** Flow chart describing data collection in the Melanoma Patterns of Care study .. 131

**Figure 6.1.** Distribution of the per patient cost to the health care system for 12 months of surveillance at the High Risk Clinic ($AU).................................................................133

**Figure 7.1.** Two-way sensitivity analysis for the probability of an excision in , specialised surveillance compared with probability of excision in standard care.................................173

**Figure 7.2.** Incremental cost-effectiveness, specialised surveillance v. standard care........174
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>APDC</td>
<td>Admitted Patient Data Collection</td>
</tr>
<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
</tr>
<tr>
<td>AUD</td>
<td>Australian dollar</td>
</tr>
<tr>
<td>BCC</td>
<td>Basal cell carcinoma</td>
</tr>
<tr>
<td>NSW CR</td>
<td>New South Wales Cancer Registry</td>
</tr>
<tr>
<td>CHeReL</td>
<td>The Centre for Health Record linkage</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CT</td>
<td>X-ray computed tomograph</td>
</tr>
<tr>
<td>HREC</td>
<td>Health Research Ethics Committee</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health related quality of life</td>
</tr>
<tr>
<td>HRC</td>
<td>High Risk Clinic</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
</tr>
<tr>
<td>M</td>
<td>AJCC staging for melanoma: Distant metastasis</td>
</tr>
<tr>
<td>MBS</td>
<td>Medicare Benefits Scheme</td>
</tr>
<tr>
<td>N</td>
<td>AJCC staging for melanoma: Regional Lymph nodes</td>
</tr>
<tr>
<td>NA</td>
<td>Not applicable</td>
</tr>
<tr>
<td>NEAF</td>
<td>National Ethics Application Form</td>
</tr>
<tr>
<td>NOS</td>
<td>Not otherwise specified</td>
</tr>
<tr>
<td>NSW</td>
<td>New South Wales</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PHSREC</td>
<td>The NSW Population and Health Services Research Ethics Committee</td>
</tr>
<tr>
<td>QALYs</td>
<td>Quality-adjusted life-years</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SCC</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SDDI</td>
<td>Sequential digital dermoscopy imaging</td>
</tr>
<tr>
<td>SSWAHS</td>
<td>Sydney South West Area Health Service</td>
</tr>
<tr>
<td>SURE</td>
<td>Secure unified research environment</td>
</tr>
<tr>
<td>T</td>
<td>AJCC staging for melanoma: Primary tumour</td>
</tr>
<tr>
<td>TBP</td>
<td>Total body photography</td>
</tr>
<tr>
<td>SURE</td>
<td>Secure unified research environment</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
</tbody>
</table>
Abstract

Clinical guidelines recommend that people at high risk of melanoma receive regular surveillance, as prognosis is better if melanomas are detected at an early stage. In this thesis, I conducted a systematic review of international clinical practice guidelines for identification, screening and follow-up of individuals at high risk of primary cutaneous melanoma, and analysed population-based data on their characteristics and actual management practices using data from the New South Wales Melanoma Patterns of Care study. I found a high degree of variation in international guidelines regarding identification and follow-up recommendations, mainly due to low levels of evidence. From the MPOC study, I found that age at diagnosis and body site of the melanomas differed according to patients’ specific risk factors. The main body of work in this thesis concerned the evaluation of the costs and benefits of a specialised ‘High Risk Clinic’ for surveillance of people at very high risk of melanoma, using data from the Clinic and a population-based dataset comprising linked data from various sources. My research built on a previous study that found melanomas were detected at an early stage and excision rates were reduced using the High Risk Clinic protocol. First, I undertook a micro-costing study to understand service delivery and costs of a High Risk Clinic. The mean annual health system cost of $1,009 per patient was comparable with the societal costs of $972 reflecting the time patients spent attending the clinic. Then, to examine the cost-effectiveness of the High Risk Clinic, I built a decision-analytic model to compare the costs and benefits of the Clinic compared to standard care in the community. I found that surveillance through the High Risk Clinic was both less expensive and more effective than standard care. Over ten
years, the mean saving was AUD $8,451 (95% CI $7,174-$9,719) per patient, and the mean quality-adjusted life year (QALY) gain was 0.31 (95% CI 0.27-0.35). The main drivers of the differences were detection of melanoma at an earlier stage resulting in less extensive treatment, and a lower annual mean excision rate for suspicious lesions in the High Risk Clinic compared to standard care. The findings in this thesis have important policy and practice implications for the management of people at high risk of melanoma.
Thesis themes and structure

Thesis aim

The aims of this thesis were to:

i) Review and summarise practice guidelines for the management of people at high risk of melanoma.

ii) Describe the management of high risk melanoma patients within NSW.

iii) Describe the characteristics of high risk melanoma patients in NSW.

iv) Determine the mean per patient costs of surveillance in a High Risk Clinic from a health service and societal perspective.

v) Evaluate the cost-effectiveness of the High Risk Clinic compared with standard care from a health service perspective.

Structure and summary of the thesis

The thesis is composed of an introduction, a methods chapter, five manuscripts and a conclusion.

Brief outline

Chapter 1. Introduction: The introduction provides some background to having a predisposition to melanoma, due to genetics and/or extensive sun exposure, and the rationale for providing a specialised clinic for people at high risk of melanoma.
Chapter 2. Methods: This chapter provides details about the Melanoma Patterns of Care study, and ethics and protocol requirements for the conduct of the cost-effectiveness study. Some of the methods not covered in detail in the papers are also included, such as the application for data linkage and ethics approvals, and additional information on measurement of quality of life assessment of clinical practice in the community.

Chapter 3. This chapter comprises a systematic review of international clinical practice guidelines on the management of people at high risk of melanoma. Clinical practice guidelines are an important resource for assisting clinicians in the management of their patients. I summarise international clinical practice guidelines and the quality of evidence for identification, screening and follow-up of individuals at high risk of primary cutaneous melanoma.

I found that while guidelines for primary treatment and staging of melanoma are relatively standardized, recommendations for identification, screening and follow-up of high-risk individuals appear to differ by country. While there was substantial variation across clinical practice guidelines regarding definition of melanoma risk factors, and definitions of ‘high-risk’ criteria, there was consensus about long-term screening, use of dermoscopy to examine suspicious lesions and education about self-examination. There was a general consensus that recommendations for screening and follow-up should change according to risk level, there was substantial variation across clinical practice guidelines regarding recommendations for screening and follow-up intervals.
Chapter 4. This chapter describes the characteristics of high risk patients in NSW using the Melanoma Patterns of Care study. I describe patient and melanoma characteristics, such as age at diagnosis, histopathological tumour characteristics and body site of the melanoma for melanoma patients with and without additional risk factors for subsequent primary melanoma. Melanoma patients with additional risk factors (as identified by the patients doctor), were classified as ‘high risk’ and those without additional risk factors were classified as ‘lower risk’.

Our results indicate that individuals with many naevi or a personal or family history of melanoma will, on average, present with melanoma at a younger age and be more likely to have melanoma on areas covered by clothing (intermittently sun-exposed sites). These higher risk individuals would likely benefit from counselling and whole-body skin checks, as offering increased skin surveillance to higher risk patients has been shown to be effective in detecting subsequent melanomas at an early stage.

Chapter 5. This chapter describes the diagnosis and clinical management of high risk individuals within NSW using the Melanoma Patterns of Care study which was a population-based, observational study based on doctors’ reported clinical management of melanoma patients in New South Wales, Australia, diagnosed with an in situ or invasive primary melanoma over a 12-month period from October 2006. At a local level I sought to describe the method of diagnosis, clinical management and adherence to clinical practice guidelines for melanoma patients at higher risk of a subsequent primary melanoma, and compare this with melanoma patients at lower risk. All patients in this study had a melanoma identified during the Melanoma Patterns of Care Study period. Those classified as being at ‘higher risk’ had
additional melanoma risk factors identified by the patient’s doctor, such as many nevi, a family history or multiple primary melanomas.

Compared to melanoma patients at lower risk, those with additional risk factors were more likely to receive initial care from a primary care physician than a specialist, have their melanoma detected during a routine skin check, their lesion assessed using dermoscopy, and to have skin surveillance and skin self-examination recommended.

**Chapter 6.** This chapter presents the micro-costing study of a specialised clinic for patients at high risk of melanoma to determine the mean per patient costs of surveillance from a health service and societal perspective. A ‘bottom up’ micro-costing methodology was used to measure resource use over a 12-month period and these costs were then modelled over a twenty year period (simulating the expected patient lifetime). All surveillance and treatment procedures were identified through direct observation, review of medical records, and interviews with staff, and valued using Australian Government scheduled fees. Societal costs included transportation and productivity losses.

The mean annual cost per patient to the health system was AU$1,009 (95%CI $911-$1,107); discounted over 20 years was AU$13,202 (95% CI $11,916-$14,485). The mean annual societal cost per patient (excluding health system costs) was AU$972 (95%CI $899-$1,045); discounted over 20 years was AU$12,721 (95%CI $12,544-$14,463). From a health system perspective, the costs of surveillance were driven by the labour costs of the clinic staff and the number of follow-up ‘extended length’ surveillance consultations required by these patients.
Patients who require more intensive treatment impact more heavily on the overall cost of the program.

**Chapter 7.** This chapter presents the results of the cost-effectiveness study of a specialised clinic for patients at very high risk of melanoma, compared with standard care. A decision-analytic model was built to compare the costs and benefits of surveillance in the High Risk Clinic compared to standard care over a 10 year period, from a healthcare system perspective. Data from the High Risk Clinic study was used and a ‘high-risk standard care’ cohort was obtained using linked population data, comprising the 45 and Up cohort study, linked to Medicare, the NSW Central Cancer Registry and the Admitted Patient Data Collection. Nearly all patients in this study had a previous melanoma and were considered at very high risk of a subsequent melanoma due to the presence of additional risk factors. A 10 year time horizon reflects the length of time in which the costs and benefits of specialised surveillance are likely to be realised. Surveillance includes management of all skin cancer lesions including keratinocytic and their diagnosis and treatment place a high burden on the healthcare system in terms of resource use and costs.

Surveillance through the High Risk Clinic was both less expensive and more effective than standard care. The mean difference was AUD $8,230 (95% confidence interval (CI) $6,962-$9,497) per patient, and the mean quality-adjusted life year (QALY) gain was 0.31 (95% CI 0.27-0.35). The main drivers of the differences were detection of melanoma at an earlier stage resulting in less extensive treatment, and a lower annual mean excision rate for suspicious lesions in the High Risk Clinic compared to standard care (0.81; 95% CI, 0.72 to 0.91 vs 2.25;
95% CI, 2.34 to 2.76 respectively). The results were unchanged when tested in sensitivity analyses.

**Chapter 8.** Discussion and conclusion: This chapter summarises the main findings of the study, addresses limitations, provides recommendations for further research arising out of this research and concludes with implications for health policy in NSW.
1 Introduction

1.1 Melanoma incidence and mortality

Melanomas are malignancies of melanocytes. The principal function of melanocytes is the production of melanin pigments to protect the skin following sun exposure. Australia and New Zealand have significantly higher age-standardised incidence rates of melanoma compared to the rest of the world. It is mandatory to report melanoma to cancer registries in Australia. In NSW, melanoma is the third most common cancer in males and females. The age standardised incidence rate was 48 per 100,000 cases for males and females in 2011. The incidence rate has remained stable over the last ten years in NSW and in 2010 there were almost 4,000 cases confirmed by the NSW Cancer Registry. In NSW in 2010, deaths from melanoma ranked 9th of all cancers. While most melanomas are diagnosed in people over 60 years, for younger people aged between 15-29 years, melanoma accounts for 26% of cancers and is the leading cause of cancer related deaths in this age group. The NSW Cancer Registry, which provided the incident melanoma data for this study, classifies an individual’s skin as a single organ. As a consequence, only the first invasive melanoma is included in their incidence figures. Information about in situ melanoma or subsequent invasive melanomas are collected, but are not reported by the Registry. Numbers of in situ melanomas as a proportion of all melanomas have been estimated at 27-43%, and subsequent invasive reports following an invasive or in situ report add another approximately 12%.
1.2 Risk factors for melanoma

Ultraviolet radiation from sunlight is an important contributor to melanoma risk. An individual’s risk of melanoma is also related to genetic and phenotypic characteristics, including fair skin, red hair, a tendency to develop freckles, naevi and dysplastic naevus syndrome, a family history of melanoma (ie. blood relatives with melanoma), or a known genetic mutation predisposing to melanoma. It has been estimated that 10% of people with melanoma have a family history. Additionally, once diagnosed with a first primary melanoma, a person is about five times more likely to develop a subsequent primary melanoma compared to the general population.

Melanoma is genetically heterogeneous and a number of genes have been identified as contributing to risk. A family history of melanoma remains an important indicator for genetic predisposition while research into identifying additional melanoma predisposition genes and the inter-relationship between melanoma and exposure to sunlight continues.

International guidelines vary in their classification of high risk. In some countries, guidelines describe the population as ‘high’ and ‘average’ risk for cutaneous melanoma, however a few guidelines have an additional category ‘very high’ or ‘extreme’ risk of cutaneous melanoma. High naevus counts, dysplastic naevi, Fitzpatrick Skin Type I or II, and family history predominated in all guidelines. The development and validation of risk prediction models will assist in clarification and identification of risk factors for cutaneous melanoma occurrence.
1.3 Staging and classification

Melanoma is staged using the American Joint Committee on Cancers (AJCC’s) TNM system to describe a cancer’s stage at diagnosis (Table 1.1). Depending on tumour thickness (T), nodal (N) and metastatic spread (M), at the stage of diagnosis melanoma is classified as in situ (stage 0), stage 1, stage 2, stage 3 or stage 4 (Table 1.2). Breslow tumour thickness is an important prognostic indicator, and 10-year survival rates are estimated to be 92% for localised melanomas less than 1mm thick, 80% for T2 melanomas (1.01-2.00 mm), 63% for T3 melanomas (2.01-4.0 mm) and 50% for T4 melanomas (>4.0 mm).
Table 1.1 American Joint Committee on Cancer (AJCC) melanoma TMN staging classification for cutaneous melanoma (7th Edition).

<table>
<thead>
<tr>
<th>T</th>
<th>Thickness</th>
<th>Ulceration status</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
<td></td>
</tr>
<tr>
<td>Tis</td>
<td>Melanoma in situ</td>
<td></td>
</tr>
</tbody>
</table>
| T1  | $\leq 1.0$ mm               | a: Without ulceration and mitosis $< 1/mm^2$  
                              | b: With ulceration or mitoses $\geq 1/mm^2$  |
| T2  | 1.01–2.0 mm                 | a: Without ulceration                   |
                              | b: With ulceration                     |
| T3  | 2.01–4.0 mm                 | a: Without ulceration                   |
                              | b: With ulceration                     |
| T4  | > 4.0 mm                    | a: Without ulceration                   |
                              | b: With ulceration                     |

<table>
<thead>
<tr>
<th>N</th>
<th>No. of metastatic nodes</th>
<th>Nodal metastatic mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>1 node</td>
<td>a: Micrometastasis</td>
</tr>
<tr>
<td>N1</td>
<td>2–3 nodes</td>
<td>b: Macrometastasis</td>
</tr>
</tbody>
</table>
<pre><code>                          | a: Micrometastasis                      |
</code></pre>
<p>| N2  | 4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes | b: Macrometastasis                     |
| N3  | 4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes | c: In transit metastases/satellites without metastatic nodes |</p>

<table>
<thead>
<tr>
<th>M</th>
<th>Site</th>
<th>Serum lactate dehydrogenase</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
<td>NA</td>
</tr>
<tr>
<td>M1a</td>
<td>Distant skin, subcutaneous or nodal metastasis</td>
<td>Normal</td>
</tr>
<tr>
<td>M1b</td>
<td>Lung metastasis</td>
<td>Normal</td>
</tr>
<tr>
<td>M1c</td>
<td>All other visceral metastasis</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>All distant metastasis</td>
<td>Elevated</td>
</tr>
</tbody>
</table>

Abbreviations NA: not applicable

aMicrometastases are diagnosed after sentinel lymph node biopsy.

bMacrometastases are defined as clinically detectable nodal metastases confirmed pathologically.
Table 1.2 American Joint Committee on Cancer (AJCC) anatomical stage groupings for cutaneous melanoma.²²

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical stage grouping</th>
<th>Pathologic stage grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>Tis N0 M0 O</td>
<td>Tis N0 M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1a N0 M0 IA</td>
<td>T1a N0 M0</td>
</tr>
<tr>
<td>IB</td>
<td>T1b N0 M0 IB</td>
<td>T1b N0 M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T2a N0 M0 IIA</td>
<td>T2a N0 M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T2b N0 M0 IIB</td>
<td>T2b N0 M0</td>
</tr>
<tr>
<td>Staging</td>
<td>T4a N0 M0 Staging</td>
<td>T4a N0 M0</td>
</tr>
<tr>
<td>IIC</td>
<td>T4b N0 M0 IIC</td>
<td>T4b N0 M0</td>
</tr>
<tr>
<td>III</td>
<td>Any T N &gt; N0 M0 IIIIA</td>
<td>T1-4a N1a M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1-4a N2a M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1-4b N1a M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1-4b N2a M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1-4a N1b M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1-4a N2b M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1-4a N2c M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1-4b N1b M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1-4b N2b M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1-4b N2c M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any T N3 M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T Any N M1 IV</td>
<td>Any T Any N M1</td>
</tr>
</tbody>
</table>

1.4 Keratinocytic cancers incidence

Keratinocytic cancers (basal cell carcinomas (BCC) and squamous cell carcinomas (SCC)) also known as non-melanoma skin cancers, have generally low mortality (representing 1.3% of all cancer deaths in 2005),²³ but are the most commonly diagnosed cancers in Australia.⁸

Keratinocytic cancers are not reportable to cancer registries in Australia.²,²³ The age-standardised rate for keratinocytic cancers was reported as 1,170 per 100,000 cases for males and females in 2002.²⁴ Of keratinocytic cancers, BCC’s are more common than SCC’s (70% and 30% respectively).²³,²⁴ Like melanoma, aetiological factors are genetic predisposition and exposure to sunlight.²⁵,²⁶ The risk of keratinocytic cancers increases with age,²³,²⁴ and the incidence is increasing world-wide particularly effecting pale skin individuals.²⁷ Patients
who have one lesion have also significantly increased (10 fold increase) risk of subsequent keratinocytic lesions.\textsuperscript{28} While excision remains the best practice for a malignant lesion, accurate diagnosis with regard to the assessment of potential invasiveness and recurrence is important for optimal treatment to reduce morbidity and to avoid unnecessary excisions.\textsuperscript{29-31} If keratinocytic cancers are large or to treat residual tumours, radiotherapy may be used alone or as adjuvant treatment.\textsuperscript{30,31} Treatment options for low risk keratinocytes include topical creams, cryotherapy and cautery.\textsuperscript{29-32}

### 1.5 Primary and secondary prevention

Currently population screening for melanoma is not recommended\textsuperscript{33} and while there are benefits from broad approach primary prevention campaigns targeting skin cancer, beneficial public health effects may take many years to become apparent.\textsuperscript{34} Currently there are some observational studies that support screening,\textsuperscript{35,36} but higher level scientific evidence required to recommend population screening is unlikely given the requirement for a randomised trial. A randomised trial of skin screening with mortality as the endpoint was planned and piloted in Queensland, Australia, but the cost of the full trial proved to be prohibitive.\textsuperscript{37} Screening has been shown to be cost-effective if targeted to high risk populations such as individuals with a strong family history\textsuperscript{38} or older males.\textsuperscript{39} One of the consequences of screening for melanoma may be over-diagnosis (detecting and treating something that would otherwise not cause harm) and over-treatment of keratinocytic lesions.\textsuperscript{40}

While guidelines for primary treatment and staging of melanoma are relatively standardized,\textsuperscript{41} recommendations for identification, screening and follow-up of high-risk
individuals differ by country.\textsuperscript{19} Australian guidelines recommend that people at high risk of melanoma be identified by health professionals as they may benefit from regular screening.\textsuperscript{42} Guidelines for follow-up after surgical treatment of a melanoma are based on the stage of diagnosis and risk of metastases; however some guidelines provide additional recommendations including that surveillance be more intensive or ongoing if patients are at high risk of a subsequent primary melanoma.

### 1.6 Costs of melanoma and keratinocytic cancers

The diagnosis and treatment of melanoma and keratinocytic cancers places a high burden on healthcare systems in terms of resource use and costs.\textsuperscript{27,32,43-45} Health system expenditure for keratinocytic lesions is influenced by the numbers of excisions and hospital admissions.\textsuperscript{46} In 2008, 61\% of total expenditure on keratinocytic lesions was for out-of-hospital care and 39\% was for admitted care.\textsuperscript{47} The Australian health care costs estimated from Medicare Benefit Schedule (MBS) item numbers for treating keratinocytic lesions were estimated to be around A$109.8 million in 2015.\textsuperscript{43}

Melanoma is less common than keratinocytic cancers but accounts for most skin cancer deaths.\textsuperscript{48} Cost of treatment varies with stage of diagnosis and morbidity, and the cost of subsequent treatment is lower when melanoma is detected at an early stage compared to an advanced stage.\textsuperscript{45,49} For example, a sentinel lymph node biopsy is based on assessment of the primary lesion. Australian guidelines recommend that sentinel node biopsy be discussed with patients who have a primary tumour 1.2-3.5 mm thick, or for patients with a tumour 0.75-1.2 mm thick if ulceration or high mitotic rate in the tumour is detected.\textsuperscript{42} Effective strategies for
early detection are warranted given that currently there is no reliable cure for metastatic melanoma and drug treatment for metastatic disease is expensive.\textsuperscript{45,49-52} Additionally, melanoma affects a disproportionate number of young people compared with other cancers,\textsuperscript{4} and there is a large impact upon years-of-life-lost and resultant loss of productivity.\textsuperscript{49,53} In Australia, in 2014 productivity loss related to metastatic melanoma was estimated at an annual loss of $276,000 for a person of working age, and an aggregate of $231.6 million in productivity losses for all patients.\textsuperscript{50} An estimation of the lifetime economic cost of skin cancer (melanoma and keratinocytic lesions) in NSW in 2010 was $536 million or $3,514 per incident case ($44,796 per melanoma and $2459 per non-melanoma diagnosis).\textsuperscript{32} Direct costs (primary care, pharmaceutical costs and hospital costs) accounted for 72\% of costs and indirect costs (morbidity and premature mortality) accounted for 28\% of costs.

1.7 The ‘High Risk Clinic’ model

Studies of high risk groups have demonstrated that regular patient review using sequential digital dermoscopy and total body photography will assist in early detection of melanoma.\textsuperscript{54-58} In order to implement and evaluate a protocol of surveillance, a specialised ‘High Risk Clinic’ was established within a hospital outpatient clinic at the Sydney Melanoma Diagnostic Centre Royal Prince Alfred Hospital, Sydney in 2006. Surveillance involved ‘extended length’ consultations at six month intervals. The consultations included a full body skin examination augmented with dermoscopy, and the use of total body photography (TBP) plus dermoscopy when indicated. TBP has been used to monitor dysplastic naevi and assists in distinguishing between pre-existing naevi and \textit{de novo melanomas}.\textsuperscript{59,60} It is estimated that between 20-40\% of melanomas are from a pre-existing naevus.\textsuperscript{59,60} When a suspicious lesion
was identified in the High Risk Clinic, the lesion was either excised, or sequential digital dermoscopy imaging\textsuperscript{61} (SDDI) of the lesion was commenced and the patient returned for ‘naevus monitoring’ in three months’ time. SDDI enables the storage of the dermoscopy image of the lesion, facilitating comparison of the image over time so that changes in morphology can be detected.\textsuperscript{62,63} This technique has been used to detect melanomas lacking the usual dermoscopic features of melanoma\textsuperscript{62,64} and to identify changes in dysplastic naevis.\textsuperscript{63,65} Surveillance also included the management of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC).

A five year review of the High Risk Clinic demonstrated that this surveillance protocol was effective in detecting melanoma at an early stage; 91\% of melanomas detected had a measured Breslow thickness of less than 1 mm resulting in low excision rates. Low excision rates in the High Risk Clinic were observed with a benign to malignant excision ratio for keratinocytic lesions and melanoma of 1.6:1.\textsuperscript{66} Contributing factors for a low excision rate could be clinical expertise and specialised monitoring equipment. Data from this five year review of the High Risk Clinic at Royal Prince Alfred Hospital were used for the cost-effectiveness analysis. This model of specialised care for patients at high risk of melanoma has been expanded to an additional three centres (a skin cancer clinic, a private dermatology practice and a second hospital clinic) in NSW to further validate the research findings. Two centres are located within Sydney and one in a regional city, Newcastle.

Patients who required additional management for metastatic disease, (apart from excision of localised recurrence or metastatic disease detected during) specialised surveillance in the
High Risk Clinic), received this care outside of the High Risk Clinic and these follow-up costs were not included in the analysis.

1.8 Economic evaluation

Economic evaluation requires the identification, measurement and valuation of costs and outcomes (benefits) of two or more strategies, which are then compared. Based on the perspective chosen by the analyst, the unit cost of all resources required for the intervention and its downstream consequences should be included in the analysis. There are three main types of economic evaluation, cost benefit analysis, cost effectiveness analysis and cost utility analysis. In a cost benefit analysis, costs and benefits are measured in the same units. This can be problematic when ‘benefits’ are measured in monetary terms to calculate the total benefits. However the net benefits of programs can be easily compared. A cost effectiveness analysis measures the benefits in natural units and relative efficiency is assessed using an incremental ratio, (i.e cost per life year saved). These results cannot be easily compared with another health program if the incremental benefits are in different units (i.e a cost per life saved). A utility based measure of benefits overcomes some of these problems as this measure incorporates a more general measure of preference for health and well-being taking into account the impact of treatment on their quality and length of life. This health utility score is multiplied by the period of time spent in a particular health state over one year to produce a quality-adjusted life-year (QALY). Relative efficiency can be assessed as a cost per QALY. A cost utility analysis also uses utility based measures and relative utility is assessed using an incremental cost utility ratio. The QALY is the most frequently used generic measure of health outcomes in economics evaluations and is favoured because it captures both a measure of a person’s quality of life and their length of life.
Health utilities are related but distinct from other health related quality of life (HRQoL) scores as they are measures of preference for distinct health states under conditions of uncertainty, which are valued by the general population and described on an interval scale ranging from 1 for perfect health and 0 for death. In order to measure the outcomes or benefits of a program, HRQoL scores are based on the notion of an individual’s value of and preference for quality of life are required. HRQoL scores are usually disease and population specific and obtained from three main types of scale: 1) disease specific, 2) general health profiles or 3) preference based.

An economic model assists with the conceptualisation of a health care process or disease to provide information regarding the allocation of resources. Decision analytic models are a modelling technique for economic evaluation that allows for the synthesis of data from multiple sources and for various pathways or health care scenarios to be compared over time using mathematical techniques. The most commonly used decision analytic models for economic evaluations are Markov models. A Markov model allows for the movement of a cohort of people, in this case patients through a variety of pathways based on the probabilities of events occurring over a set period of time. The pathways contain a number of health states through which patient’s transition. Each health state has assigned costs and health utilities to reflect the costs and consequences of the clinical event being described. In a Markov model, costs and quality adjusted life years (QALYs) can be accumulated at each cycle.
Using a model to estimate the effects of an intervention over a number of years means that long-term clinical outcomes can be estimated. Because society has a higher preference for benefits now, compared to the future, there is a higher value placed on current time compared to the future. Future costs and QALYs are discounted to provide a present value of costs and benefits. In a cost-effectiveness study, the differences in the costs and effects (health benefits) between two strategies are measured to calculate an incremental cost-effectiveness ratio. Sensitivity analysis allows for the uncertainty around data estimates to be tested. A mean cost per QALY allows for comparison with other services using the same metric.

1.9 Cost-effectiveness analysis

In order to inform health policy decisions relating to surveillance strategies for high risk individuals, evidence of the cost-effectiveness of the High Risk Clinic model of care is required. In addition, data are required to address concerns about potential over-treatment of suspicious skin lesions, as unnecessary excisions of keratinocytic lesions place a high burden on the healthcare system in terms of resource use and costs. In Chapter 5, the costs and benefits of a specialised High Risk Clinic compared to standard care, defined as the usual care provided to high risk individuals in the community, are evaluated. Decision analytic models have been used successfully to compare different strategies in the management of melanoma. For my analysis, a Markov model was developed to conceptualise both the treatment pathway for a patient attending for surveillance of their skin and also for the melanoma disease process.
A health system perspective was chosen for the evaluation of cost-effectiveness of the High Risk Clinic. A 10 year time horizon was chosen because the costs and benefits of specialised surveillance were likely to be realised within this timeframe. All levels of governments are providers of health care in Australia\textsuperscript{76}. Many hospital, medical and pharmaceutical services, are subsidized through Medicare,\textsuperscript{77} provided by the Australian Government.\textsuperscript{78} This perspective is also relevant as health system expenditure affects budget allocation decisions. Resource allocation has an associated opportunity cost meaning when a decision is made to invest in one service, those resources are not available for allocation to another service. The opportunity cost is the value of the next best alternative forgone. Evidence that melanoma surveillance for high risk persons was cost-effective compared to currently available services would provide decisions makers with evidence for potential savings if funding was provided for high risk persons to be channelled into a surveillance program.
References


2 Methods

2.1 Preamble

This chapter provides a summary of the methods used in this thesis. Some of this information is also covered in the relevant publications/chapters, but additional details are provided here, particularly with regards to the data linkage process.

2.2 The Melanoma Patterns of Care study

The Melanoma Patterns of Care study was a population-based, observational study based on doctors’ reported management of melanoma patients residing in NSW, Australia. Patients had a new histopathologically confirmed primary in situ or invasive cutaneous or unknown primary site melanoma (ICD-O-3 site codes C44.0 to C44.9 and C80.9 (Table 2.1); morphology codes 8720-8790 /2 or /3 (Table 2.2))\(^1\) reported to the NSW Cancer Registry between 23 October 2006 and 22 October 2007. Patient demographic information and the degree of spread of the melanoma was obtained from the registry. Ethics approval was granted by the Human Research Ethics Committees of The University of Sydney and the Cancer Institute NSW.

2.2.1 Data collection

The ‘doctor providing initial care following diagnosis’ for this study was the referring doctor on the diagnostic pathology report on which the cancer registration was based. It is mandatory for pathologists in NSW to notify every newly diagnosed cancer to the Central
Cancer Registry, which they do by sending copies of pathology reports of newly diagnosed cancers. For each new melanoma case reported during this period, the doctor providing initial care was contacted by the study team and asked to complete a questionnaire regarding the clinical management of their patient. Doctors to whom the initial doctor referred a melanoma patient were also contacted by the study team and asked to complete a questionnaire. Whilst all invasive melanomas were captured and followed during the study period, questionnaire responses were only sought for the first 450 notifications of in situ melanomas, to minimise doctors’ workload. Field workers assisted with completion of questionnaires using documented patient records, when requested by doctors with large numbers of patients.

Table 2.1. List of the International Classification of Diseases for Oncology topography codes for body site of melanoma diagnosis used in the Melanoma Patterns of Care Study

<table>
<thead>
<tr>
<th>Code</th>
<th>Body site description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C44</td>
<td>Skin</td>
</tr>
<tr>
<td>C44.0</td>
<td>Skin of lip, NOS(^a)</td>
</tr>
<tr>
<td>C44.1</td>
<td>Eyelid</td>
</tr>
<tr>
<td>C44.2</td>
<td>External ear</td>
</tr>
<tr>
<td>C44.3</td>
<td>Skin of other and unspecified parts of face</td>
</tr>
<tr>
<td>C44.4</td>
<td>Skin of other and unspecified parts of face</td>
</tr>
<tr>
<td>C44.5</td>
<td>Skin of trunk</td>
</tr>
<tr>
<td>C44.6</td>
<td>Skin of upper limb and shoulder</td>
</tr>
<tr>
<td>C44.7</td>
<td>Skin of lower limb and hip</td>
</tr>
<tr>
<td>C44.8</td>
<td>Overlapping lesion of skin</td>
</tr>
<tr>
<td>C44.9</td>
<td>Skin, NOS(^a)</td>
</tr>
<tr>
<td>C80</td>
<td>Primary site unknown</td>
</tr>
<tr>
<td>C80.9</td>
<td>Malignant neoplasm, primary site unspecified</td>
</tr>
</tbody>
</table>

\(^a\) NOS: not otherwise specified.
<table>
<thead>
<tr>
<th>Code</th>
<th>Melanoma description</th>
</tr>
</thead>
<tbody>
<tr>
<td>8720/2</td>
<td>Melanoma in situ</td>
</tr>
<tr>
<td>8720/3</td>
<td>Malignant melanoma, NOS(^a)</td>
</tr>
<tr>
<td>8721/3</td>
<td>Nodular melanoma</td>
</tr>
<tr>
<td>8722/3</td>
<td>Balloon cell melanoma</td>
</tr>
<tr>
<td>8723/3</td>
<td>Malignant melanoma, regressing</td>
</tr>
<tr>
<td>8730/3</td>
<td>Amelanotic melanoma</td>
</tr>
<tr>
<td>8740/2</td>
<td>Malignant melanoma in junctional nevus</td>
</tr>
<tr>
<td>8740/3</td>
<td>Malignant melanoma in precancerous melanosis</td>
</tr>
<tr>
<td>8741/3</td>
<td>Malignant melanoma in precancerous melanosis</td>
</tr>
<tr>
<td>8742/2</td>
<td>Lentigo maligna, Hutchinson melanotic freckle, NOS(^a)</td>
</tr>
<tr>
<td>8742/3</td>
<td>Lentigo maligna melanoma, Malignant melanoma in Hutchinson melanotic freckle</td>
</tr>
<tr>
<td>8743/3</td>
<td>Superficial spreading melanoma</td>
</tr>
<tr>
<td>8744/3</td>
<td>Acral lentiginous melanoma, malignant</td>
</tr>
<tr>
<td>8745/3</td>
<td>Desmoplastic melanoma, malignant Neurotropic melanoma, malignant Desmoplastic melanoma, amelanotic</td>
</tr>
<tr>
<td>8746/3</td>
<td>Mucosal lentiginous melanoma</td>
</tr>
<tr>
<td>8761/3</td>
<td>Malignant melanoma in giant pigmented nevus Malignant melanoma in congenital melanocytic nevus</td>
</tr>
<tr>
<td>8770/3</td>
<td>Mixed epithelioid and spindle cell melanoma</td>
</tr>
<tr>
<td>8771/3</td>
<td>Epithelioid cell melanoma</td>
</tr>
<tr>
<td>8772/3</td>
<td>Spindle cell melanoma, NOS(^a)</td>
</tr>
</tbody>
</table>

\(^a\) NOS: not otherwise specified.
2.2.2 Selection of a high risk group

Questionnaires (see Appendices 9.1) were completed for 2,758 patients diagnosed with melanoma during the study period from which 1,052 (38%) patients were defined as being at higher risk of melanoma as their questionnaires indicated them as having either: 1) multiple primary melanoma (i.e. a previous melanoma before the study period), and/or 2) a family history of melanoma, and/or 3) many naevi. The remaining 1,675 (61%) patients were defined as lower risk with no additional risk factors identified. An additional 31 (1%) patients presenting with stage III disease did not have risk status data available. Assessment of the higher risk group, and comparison with the lower risk group and by type of risk factor was the basis of two papers in this thesis: Chapter 4 on characteristics of individuals and the clinical features associated with their melanomas, according to risk factor status, and Chapter 5 on diagnosis and clinical management of melanoma. The 153 (5%) patients who were diagnosed with Stage III disease were excluded from the paper examining diagnosis and management as it was thought that patient management of metastatic disease would be different to management of localised disease. For 22 patients who were diagnosed with multiple primary melanomas during the study period, the thickest lesion was chosen for analysis.

2.3 Micro-costing study

To conduct the micro-costing study, I observed the melanoma High Risk Clinic over a 10-week period, December 2012–March 2013, to understand the personnel and procedures involved in the surveillance process of the High Risk Clinic, and to identify and measure resource use related to patients and the health system. Patients participating in the High Risk Clinic had previously given their consent for collection of data under the original ethics
approval “Protocol NoX11-0409, HREC/11/RPAH/636”. An amendment was made to the protocol for me to attend the High Risk Clinic and conduct the micro-costing study which was granted by Sydney South West Area Health Service. It was noted that this study was a part of the cost-effectiveness study under review by the NSW Population and Health Services Research Ethics Committee. (Table 2.3 and Appendices 9.3).

2.4 Cost-effectiveness of the High Risk Clinic

In order to establish if the High Risk Clinic model was a value-for-money alternative to what currently exists in the community, an economic evaluation was required to compare the costs and effectiveness of both strategies. This involved identifying and estimating resource use and health outcomes.

High Risk Clinic data were available to estimate resource use, particularly for the number and type of lesions excised or treated, and the probability of melanoma stage at diagnosis. However, the High Risk Clinic study was not a randomised controlled trial. In order to obtain data for a comparator arm, it was necessary to construct a dataset to resemble standard care using population-based data from which resource use and effectiveness could be calculated (refer to the Supplementary materials in Chapter 7 for further information).

2.4.1 Data linkage

Using the data linkage key provided by the Centre for Health Record Linkage (CHeReL), a cohort of high risk patients receiving standard care in the community were selected based on 1) a reported family history of two first degree relatives with melanoma (from the 45 and Up
study) and a confirmed personal history of invasive melanoma (from the NSW Cancer Registry data), or 2) a personal history of at least two confirmed invasive melanomas in the past 10 years (from the Cancer Registry data). As the 45 and Up cohort study,\(^2\) is linked to population health data from the Medicare Benefits Schedule,\(^3\) we were able to examine health service utilisation for the standard care group over a similar treatment period to the high risk clinic group, to calculate the number and type of excisions and treatments that they received based on the Medicare Benefits item number classifications (melanoma, keratinocytic lesions, benign lesions or incision biopsy). The New South Wales Cancer Registry was also used to estimate the probability of melanoma and stage of diagnosis over five years and this was linked to the Admitted Patient Data Collection for the calculation of hospital costs. More information about the datasets can be found in Chapter 7 supplementary materials.

To obtain a linked dataset through the Centre for Health Record Linkage (CHeReL), approval from the data custodians responsible for managing their institutions data must be obtained.\(^4\) The custodians provide patient level demographic data to the CHeReL for the initial linkage, and once eligible patients are identified, a linkage key specific to the study is created by the CHeReL. The original data with a linkage key attached to the relevant patients is returned to the custodian. The custodian then removes the patient demographic data and creates a data set of patients with the study linkage key and requested variables to be provided to the researcher. The consent process for obtaining linked data for the cost-effectiveness study is outlined in Table 2.3 and ethics approval and protocol are shown in the Appendices 9.2 and 9.3. The costs for data linkage services provided by the CHeReL and access to the Secure Unified Research Environment (SURE), a remote access data laboratory, for access to the 45 and Up study data, were covered by a Sydney Catalyst Top Up Scholar award to Caroline Watts. In addition, consent was sought from the NSW Melanoma Patterns of Care
investigators to obtain a separate dataset representing individuals at higher risk of melanoma in the community. This dataset was used for the cost-effectiveness study to examine management patterns in standard care, and to cross-check the validity of information from the linked dataset.
## Table 2.3 Timeline of applications and permissions for access to the linked dataset

<table>
<thead>
<tr>
<th>Date</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2012</td>
<td>National Ethics Application Form (NEAF) submitted NSW National Ethics Application Form, v2, submission code AU/1/FD7D013.</td>
</tr>
<tr>
<td>March 2012</td>
<td>Applications to data custodians: 45 and Up study, NSW Cancer Registry, Admitted Patient Data Collection for data to be linked by the Centre for Health Record Linkage.</td>
</tr>
<tr>
<td>May 2012</td>
<td>Application to Centre for Health Record Linkage: NEAF AU/1/FD7DOB to facilitate creation of data linkage key. Application for data, Variable lists for requested data items (45 and Up study, Cancer Registry, Admitted Patient Data), NEAF, Protocol for cost-effectiveness of High Risk Clinic study (Version 1).</td>
</tr>
<tr>
<td>May 2012</td>
<td>The 45 and Up Study Data Use Agreement submitted for endorsement from the Office of General Council at the University of Sydney for student use and sign off of the 45 and Up Study Data Use Agreement.</td>
</tr>
<tr>
<td>June 2012</td>
<td>Data custodian approval received for use of data from Cancer Registry, Admitted Patient Data Collection and The 45 and Up study.</td>
</tr>
<tr>
<td>July 2012</td>
<td>Application for data linkage approved and submitted to Centre for Health Record Linkage.</td>
</tr>
<tr>
<td>July 2012</td>
<td>Human Research Ethics Committee (HREC) at the Cancer Institute NSW submission: Ethics Application Documents for NEAF AU/1/F07D013, Application includes Request for data linkage, 45 and Up study data use approval, Admitted Patient Data Collection data use approval, Cancer Registry data use approval, NEAF, Protocol (Version 1).</td>
</tr>
<tr>
<td>October 2012</td>
<td>Approval for use of The 45 and Up Study data from the University of Sydney and sign off by researchers to The 45 and Up study.</td>
</tr>
<tr>
<td>October 2012</td>
<td>Approval HREC Ethics Application for use of data from Melanoma Patterns of Care and High Risk Clinic study (external data) Protocol (Version 2).</td>
</tr>
<tr>
<td>August 2012</td>
<td>Approval from Sydney South West Area Health Service to attend High Risk Clinic and conduct micro-costing study.</td>
</tr>
<tr>
<td>February 2013</td>
<td>Admitted Patient Data provided – data set incomplete as one column of procedure data was not included and there was no patient data for 2010.</td>
</tr>
<tr>
<td>March 2013</td>
<td>Cancer Registry data provided – data incomplete as all subsequent invasive reports were not included.</td>
</tr>
<tr>
<td>April 2013</td>
<td>Approval HREC Ethics application approved to access linked data using the Secure Unified Research Environment. Protocol (Version 2).</td>
</tr>
<tr>
<td>May 2013</td>
<td>Admitted Patient Data 2010 provided.</td>
</tr>
<tr>
<td>July 2013</td>
<td>Approval from the HREC to obtain requested multiple reports of invasive melanoma Protocol (Version 3).</td>
</tr>
<tr>
<td>September 2013</td>
<td>Approval HREC Ethics application to move Cancer Registry data and Admitted patient data from the University of Sydney to the Secure Unified Research Environment (SURE), remote access data base, supported by the Sax Institute. Protocol (Version 4).</td>
</tr>
<tr>
<td>October 2013</td>
<td>Approval HREC Ethics application to access data using the SURE and Sydney University. Protocol (Version 4)</td>
</tr>
<tr>
<td>October 2013</td>
<td>Admitted Patient Data procedure data provided – data set complete.</td>
</tr>
<tr>
<td>October 2013</td>
<td>Approval HREC Ethics application for change in CI from C Watts to Dr A Cust as requested by Cancer Institute as condition for use of subsequent invasive melanoma reports. Protocol (Version 5).</td>
</tr>
<tr>
<td>December 2013</td>
<td>Cancer Registry multiple reports provided - Cancer Registry complete.</td>
</tr>
</tbody>
</table>

2.4.2 Cost-effectiveness evaluation

A Markov model was developed for this analysis using TreeAge Pro 2015, R1.0 (TreeAge Software, Williamstown, MA). The model, based on annual cycles over a ten year period, was able to account for various scenarios (health outcomes and incurred costs) following a cohort of patients presenting for annual surveillance in standard care or at the High Risk Clinic, the potential excision of a suspicious lesion, and diagnosis and treatment of melanoma. In one year, more than one lesion could be identified as suspicious and excised, and diagnosed as either a histo-pathologically confirmed melanoma, keratinocytic or benign lesion. If a melanoma was not diagnosed, a patient would present for surveillance at the beginning of the next cycle. If a melanoma was diagnosed, based on the stage at diagnosis and probability of recurrence, either the patient would present for surveillance at the beginning of the next cycle or a number of disease and treatment scenarios could eventuate (diagrams of the decision tree and Markov model are in the Supplement section of Chapter 7). All health states had associated costs and utilities. The six health states are 1. Patient presents for surveillance, 2. Recurrence of melanoma, 3. Stage III disease, 4. Stage IV disease, 5. Dead due to melanoma, 6. Dead due to other causes. More information on the model is shown as Figures on pages 187-8. The multiple service rule in the Medicare Benefits schedule was applied to multiple excisions by lesion type, and pathology item numbers were based on the number of annual excisions. Probabilities of melanoma by stage at diagnosis and excision combinations were assumed to be constant over time. For the High Risk Clinic arm, probabilities of a new melanoma by stage at diagnosis, and of excisions, were obtained from the High Risk Clinic Study dataset. For the standard care arm, NSW Cancer Registry data were used to calculate the probability of a new melanoma by stage at diagnosis, and linked MBS data were used to examine resource use and calculate the probability of excisions.
In the Markov model, there was provision of numerous options for treatment within the cycle, such as variation in lesions excised and transitions to more advanced stages of melanoma. Using annual cycles with a range of alternatives helped address the limitations of the memory-less nature of the Markov chain, whereby patients move between health states based on the probabilities of being in the previous health state, so probabilities are independent of past events. However, sometimes in real life, events are not independent of past events. Other novel adaptations that I performed in this study were the use of a tunnel calculation feature in ‘Treeage’ so that costs for screening, for example, can decrease over time, and making the risk of non-melanoma related death age-dependent. We also undertook sensitivity analyses examining all variables independently (one way sensitivity analysis), by comparing the interaction between two variables (two way sensitivity analysis), and probabilistic sensitivity analysis to test the effect of a range of variables on the model results.

2.4.3 Quality of life measure

In order to compare the two surveillance alternatives, I undertook a review of studies that reported utility weights applied for melanoma patients. (Appendix 9.4) Because of the annual cycle period of the model, weights that could be applied to both diagnosis and the interval following treatment, which would vary according to the stage at diagnosis, were preferred. As such, health utilities were chosen from a study by Tromme et al, based on melanoma patients’ preference for survival and valuation of their quality of life at all stages of diagnosis (including in-situ melanoma) and following treatment. These weights were considered the most suitable of those published and were relevant to the types of treatment and procedures used in Australia. Additionally, in the study by Tromme et al, patients completed a range of
questionnaires concurrently: the EuroQoL Five Dimensions Five Levels (EQ-5D-5L) questionnaire, the EuroQoL visual analogue scale (VAS), and Functional Assessment of Cancer Therapy Melanoma (FACT-M), enabling the results to be validated against standard measures. Utility weights were also disease-specific and applied to patients undergoing diagnosis and excision of keratinocytic lesions\textsuperscript{8,9} (Appendix 4).

2.4.4 Removal of duplicate records

Two methods were used to remove high risk clinic patients who also appeared to be in the standard care data set.

1. Cancer registry dataset variables were age at diagnosis, sex, month of diagnosis and year of diagnosis, morphology and topography. Date of birth was not provided. A range of age variables were calculated for each patient, adding and deducting a year from age at diagnosis. Deterministic matching, progressively matching the variables month of diagnosis, year of diagnosis, morphology, topography, sex and age at diagnosis to the same High Risk Clinic variables, was used to select matching records.

2. High Risk Clinic (HRC) dataset multiple records were selected and matched to standard care records on sex and year of diagnosis and then on year of diagnosis and month of diagnosis.

Of the twenty records identified in both search strategies, 10 records were found by both search strategies and 10 records were unique to each search. Thus, in total, 30 records were removed from the standard care dataset as they were likely to be High Risk Clinic patients. The final standard care dataset was reviewed for duplicate records and two patients had the same cancer record which was identified as duplicate and removed.
2.4.5 **Surveillance cost for patients in standard care data set**

To estimate the cost of a skin examination based on the clinical pathway for the standard care arm of the model, I conducted a telephone survey of 10 skin cancer clinics and general practice clinics in Sydney and major towns in NSW in November 2014. I asked the receptionist about the usual MBS item numbers that would be used when a patient made an appointment for a skin examination (Appendix 9.5). The most common consultation type was Level C (*MBS item number* 36), reflecting a visit to a doctor between 20-40 minutes in duration, was used in the model.

2.4.6 **Estimation of the cost of death due to melanoma**

The estimated cost of dying from melanoma was based on the average time a patient spends in a palliative care facility in Australia.\(^{10,11}\)

2.4.7 **Estimation of the cost of death due to causes other than melanoma**

The estimated cost of dying was based on health system costs for older patients admitted to hospital in their last year of life.\(^{12}\) This figure was halved based on 50% of people dying in hospital.\(^{11}\) We did not include an additional cost of dying for the 35% of patients who died while in residential care or those who died at home. Costs were calculated in 2013 dollars using published deflators.\(^{13}\)
2.5 References


3 Clinical practice guidelines for identification, screening and follow-up of individuals at high risk of primary cutaneous melanoma: a systematic review

3.1 Preamble

This chapter provides a systematic review of 34 clinical practice guidelines from around the world regarding recommendations for the identification, screening and management of individuals at higher risk of developing melanoma.
Clinical practice guidelines for identification, screening and follow-up of individuals at high risk of primary cutaneous melanoma: a systematic review*

C.G. Watts,1 M. Dieng,1 R.L. Morton,2,3 G.J. Mann,4 S.W. Menzies5 and A.E. Cust1

1Cancer Epidemiology and Services Research (CESR), 2Sydney School of Public Health, The University of Sydney, Australia
4University of Sydney at Westmead Millennium Institute and Melanoma Institute Australia, Sydney, Australia
5Sydney Melanoma Diagnostic Centre, Sydney Cancer Centre, Royal Prince Alfred Hospital and the Sydney Medical School, Discipline of Dermatology, The University of Sydney, Australia

Summary

Understanding how individuals at high-risk of primary cutaneous melanoma are best identified, screened and followed up will help optimize melanoma prevention strategies and clinical management. We conducted a systematic review of international clinical practice guidelines and documented the quality of supporting evidence for recommendations for clinical management of individuals at high risk of melanoma. Guidelines published between January 2000 and July 2014 were identified from a systematic search of Medline, Embase and four guideline databases; 34 guidelines from 20 countries were included. High-risk characteristics that were consistently reported included many melanocytic naevi, dysplastic naevi, family history, large congenital naevi, and Fitzpatrick Type I and II skin types. Most guidelines identify risk factors and recommend that individuals at high risk of cutaneous melanoma be monitored, but only half of the guidelines provide recommendations for screening based on level of risk. There is disagreement in screening and follow-up recommendations for those with an increased risk of future melanoma. High-level evidence supports long-term screening of individuals at high risk and monitoring using dermoscopy. Evidence is low for defining screening intervals and duration of follow-up, and for skin self-examination, although education about skin self-examination is widely encouraged. Clinical practice guidelines would benefit from a dedicated section for identification, screening and follow-up of individuals at high risk of melanoma. Guidelines could be improved with clear definitions of multiple naevi, family history and frequency of follow-up. Research examining the benefits and costs of alternative management strategies for groups at high risk will enhance the quality of recommendations.

What’s already known about this topic?

- The rationale for screening and follow-up of people at high risk of melanoma is that earlier diagnosis leads to decreased morbidity, medical costs and patient anxiety.

What does this study add?

- A summary of risk factors for ‘high’ and ‘very high’ risk groups.
- A summary of the levels of evidence for different clinical recommendations aimed at individuals at high risk.
A systematic review that demonstrates there is variation on definitions of high risk; and disagreement about recommendations for screening methods or follow-up based on the level of risk for a future cutaneous melanoma.

In most countries with populations of predominantly European origin, incidence rates of cutaneous melanoma have increased over the past decade.\textsuperscript{1,2} The general rationale for screening and follow-up of people at high risk of melanoma is based on evidence that earlier diagnosis leads to decreased morbidity,\textsuperscript{3} reduced medical costs\textsuperscript{4} and decreased anxiety.\textsuperscript{5} Population screening is currently not recommended in most countries.

Understanding how individuals at high risk of primary cutaneous melanoma are best identified, screened and followed up will help optimize melanoma prevention strategies and clinical management of melanoma. This includes uncertainty about which groups in the general population should be monitored more closely, and what the efficient optimal screening and follow-up intervals are from health outcomes and economic perspectives.\textsuperscript{6–8} Unlike guidelines for primary treatment and staging of melanoma, which are relatively standardized,\textsuperscript{9} recommendations for follow-up after a melanoma diagnosis appear to differ by country.\textsuperscript{10}

The aim of this systematic review was to examine international clinical practice guidelines for identification, screening (prior to melanoma diagnosis) and follow-up (after melanoma diagnosis) of individuals at high risk of primary cutaneous melanoma, and the quality of the evidence supporting their recommendations. Our purpose was to identify areas of strength and weakness in this evidence base and therefore inform scientific and clinical discussion regarding the management of individuals at high risk of melanoma. We did not address recommendations for management of congenital naevi, follow-up for local, regional or distant recurrence, or recommendations relating to family members.

**Methods**

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)\textsuperscript{11} checklist.

**Data sources**

Two separate strategies were used to identify clinical practice guidelines published between January 2000 and July 2014. Firstly, we performed a literature search for guidelines using Medline (‘melanoma.mp’ AND ‘practice guideline’) and Embase (‘melanoma’/exp AND ‘practice guideline’/de). Secondly, we searched the following guideline databases using the search term ‘melanoma’:


2. Turning Research Into Practice (Trip) Database

3. National Guideline Clearinghouse database based within the Agency for Healthcare Research and Quality (AHRQ)

4. Canadian Medical Association (CMA) Clinical Practice Guidelines Database.

**Study selection**

Titles and abstracts from Medline and Embase were screened and the full text of potentially relevant manuscripts was examined to identify relevant guidelines. The guideline databases mainly contained clinical recommendations and provided a reference to the country and organization responsible for the recommendations. In all cases, we attempted to source the original and most recently published guideline. We included guidelines that focused on prevention or risk factors for cutaneous melanoma, identification of individuals at high risk of melanoma, or included management of patient care in relation to melanoma screening or follow-up. When there was a range of guidelines from a single country, we selected national guidelines that had been created by government health organizations and nationally recognized professional groups (e.g. American Academy of Dermatology). If national guidelines were not available, we included regional guidelines created by a guidelines committee or group of referring centres, or guidelines produced by opinion leaders or referring centres that were targeted at healthcare professionals.

Based on the title and abstract, publications were excluded if:

1. the guidelines had a singular focus on pathology, oncology or surgical techniques related to melanoma diagnosis or treatment

2. the guidelines did not include recommendations for cutaneous melanoma

3. they were described by the authors as a review, overview or guide

4. guidelines were superseded by a later publication from the same authors or group

5. the intended audience was the general public or a specific specialist group (e.g. nurses).

When eligibility for inclusion in the review was unclear, the guidelines were discussed with co-authors A.E.C. and R.L.M. and selection agreed by consensus. If the guideline could not be sourced in English, Google Translate (www.translate.google.com.au) was used for translation.
Data extraction

From the clinical practice guidelines, we extracted information regarding the following:

1. Description of melanoma risk factors, particularly identification of high-risk groups. For follow-up, we selected risk factors for development of a subsequent primary melanoma.
2. Recommendations for screening prior to melanoma diagnosis, and follow-up after melanoma diagnosis for a subsequent primary melanoma and whether there was a specific recommendation for ‘high-risk’ groups.
3. The intended audience and quality of evidence supporting the recommendations.

We summarized and collated the key clinical recommendations in the guidelines.

Quality assessment of the evidence supporting the guideline recommendations

To standardize the levels of evidence stated in each guideline, we used the Oxford Centre for Evidence-Based Medicine validated appraisal tool\(^\text{12}\) for which the evaluation of evidence was based around the question ‘what interventions are recommended in the guidelines for people at greatest risk of melanoma?’ (see Supplementary Table S1). This was considered to be the most relevant tool for the review. Levels of evidence were graded as ‘high’ if the strongest levels of evidence (i.e. level 1 or level 2) were provided, ‘low’ if the evidence was graded as level 3 or level 4, and ‘very low’ if the evidence was based on ‘mechanistic reasoning’ (level 5) including recommendations arising from expert opinion. Two reviewers (C.G.W. and M.D.) assessed the levels of evidence as stated in the original guideline. Where definitions of the levels of evidence in guidelines were similar to the Oxford definitions, levels were mapped across. Where levels were not provided (Table 1), the references cited for the recommendation were reviewed by C.G.W. and M.D. and a level of evidence was assigned using the Oxford table. When opinions differed on the level of evidence between reviewers, the guidelines were discussed and consensus reached.

Results

Literature search results

We initially identified 981 publications meeting our search criteria, and after excluding 947 ineligible publications, 34 guidelines from 20 countries were included in the review (Fig. 1). Most ineligible publications were reporting research results (e.g. related to melanoma therapies) that could have implications for guidelines, or were guidelines about specific treatments or procedures. Just over half of the guidelines (18 of 34) reviewed were produced since 2010.

Risk factor identification

Almost all (32 of 34) of the clinical practice guidelines stated that some groups in the population have an increased risk of melanoma; however, the number of risk factors identified in the guidelines varied considerably (from 0 to 17) (Table 1). These risk factors fell within four categories which could be broadly summarized as: naevi; other phenotypic features such as fair skin; ultraviolet (UV) exposure; and a miscellaneous group (e.g. history of previous melanoma, family history, rare genetic conditions and immunosuppression). There was a wide range of terminology used to describe risk factors from the general to the specific: for example multiple naevi were described as ‘many moles’, ‘increased naevi’ or ‘> 50 or 100 naevi’. While UV exposure was cited by most guidelines as a major risk factor, 12 guidelines\(^\text{13–24}\) listed indoor tanning beds as a risk factor.

We examined melanoma risk factors by region and identified which risk factors were found in more than 50% of guidelines (Fig. 2). High naevus counts, dysplastic naevi, Fitzpatrick skin type I or II,\(^\text{2,5}\) and family history predominated in all guidelines. European guidelines were different from those of North America and the Southern hemisphere as they include a history of intermittent sun exposure as a risk factor; the majority (75%) of guidelines from the Southern hemisphere countries included actinic or solar lentigines (measures of chronic sun exposure).

Definition of high-risk groups

While most guidelines mentioned risk factors, 25 (73%) recommended risk assessment for melanoma. Of these, 20 defined what was meant by risk assessment,\(^\text{13,14,16,18,19,21,23,24,26–37}\) describing this within a context of the medical history and clinical assessment of the patient or selection for screening which could occur opportunistically or when a patient attends with a suspicious lesion. Supplementary Table S2 shows a summary of the different countries’ guidelines regarding assessment of level of risk, applicable to high-risk individuals. An increase in risk due to possession of more than one risk factor was described in seven guidelines.\(^\text{13,14,20,21,23,35,37}\)

Sixteen (47%) guidelines described an ‘increased’ or ‘high’ risk group compared with the general population. Nine guidelines\(^\text{11,14,16,21,23,24,28,31,33}\) described three levels of risk: average, high and ‘very high’ or ‘extreme’ risk; these high-risk classifications are described in Table 2. Some guidelines provided summary relative risks for the different risk factors, from which we selected those conferring a relative risk > 4 as ‘very high’ risk; this cut-off point was chosen to be consistent with most guidelines that provided both relative risks and risk categories, whereby relative risks of 1–4 were generally classified as ‘high’ and relative risks above 4 as ‘very high’ risk. In general, risk factors that conferred the highest risk were: CDKN2A mutation carriers, > 100 naevi, > 5 atypical naevi, a
<table>
<thead>
<tr>
<th>Country</th>
<th>Guideline</th>
<th>Target audience</th>
<th>Screening (prior to cutaneous melanoma)</th>
<th>Follow-up (for subsequent primary lesion)</th>
<th>Evidence base for creation of guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Number of risk factors</td>
<td>Differentiation of levels of risk</td>
<td>Number of risk factors</td>
</tr>
<tr>
<td>Austria/Italy</td>
<td>Zalaudek et al. (2005)</td>
<td>Not stated</td>
<td>13</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Brazil</td>
<td>Brazilian Society of Dermatology (2005)</td>
<td>Not stated</td>
<td>0</td>
<td>No</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>BC Cancer Agency (2013)</td>
<td>Clinicians</td>
<td>11</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Canadian Expert Panel on Malignant Melanoma (2009)</td>
<td>Clinicians</td>
<td>9</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Europe</td>
<td>EDF, EADO, EORTC (2012)</td>
<td>Clinicians and healthcare specialists</td>
<td>7</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>ESMO (2012)</td>
<td>Not stated</td>
<td>1</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Finland</td>
<td>Finnish Medical Society (2012)</td>
<td>Clinicians and healthcare providers</td>
<td>7</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Country</td>
<td>Guideline</td>
<td>Target audience</td>
<td>Screening (prior to cutaneous melanoma)</td>
<td>Follow-up (for subsequent primary lesion)</td>
<td>Evidence base for creation of guideline</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------------------------------------------------------</td>
<td>--------------------------------------</td>
<td>----------------------------------------</td>
<td>------------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Number of risk factors</td>
<td>Differentiation of levels of risk</td>
<td>Number of risk factors</td>
</tr>
<tr>
<td>France</td>
<td>French National Cancer Institute (2012)</td>
<td>Clinicians</td>
<td>13</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>French Society of Dermatology (2007)</td>
<td>All healthcare professionals</td>
<td>0</td>
<td>No</td>
<td>3</td>
</tr>
<tr>
<td>Germany</td>
<td>German Dermatologic Society; Dermatologic Cooperative Oncology Group (2013)</td>
<td>All healthcare professionals</td>
<td>11</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Italy</td>
<td>Italian Group of Dermatology and Oncology and Multidisciplinary Group on Melanoma (2007)</td>
<td>Not stated</td>
<td>4</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Dutch Working Group on Melanoma (2013)</td>
<td>Clinicians and healthcare providers</td>
<td>11</td>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td>New Zealand</td>
<td>New Zealand Guidelines Group (2009)</td>
<td>Primary care clinicians</td>
<td>8</td>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td>Norway</td>
<td>Guidelines Working Group (2011)</td>
<td>General practitioners and specialists</td>
<td>9</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Poland</td>
<td>Rutkowski et al. (2013)</td>
<td>Not stated</td>
<td>6</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>South Africa</td>
<td>Melanoma Advisory Board (2004)</td>
<td>Physicians</td>
<td>8</td>
<td>No</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 1 (continued)

<table>
<thead>
<tr>
<th>Country</th>
<th>Guideline</th>
<th>Target audience</th>
<th>Screening (prior to cutaneous melanoma)</th>
<th>Follow-up (for subsequent primary lesion)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Number of risk factors</td>
<td>Differentiation of levels of risk</td>
</tr>
<tr>
<td>Spain</td>
<td>Mangas et al. (2010) (^{11})</td>
<td>Clinicians</td>
<td>13</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Villalobos León et al. (2013) (^{12})</td>
<td>Not stated</td>
<td>14</td>
<td>No</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Dummer et al. (2012) (^{12})</td>
<td>Clinicians</td>
<td>7</td>
<td>No</td>
</tr>
<tr>
<td>Ukraine</td>
<td>Guidelines Working Group (2014) (^{14})</td>
<td>Specialists and family doctors</td>
<td>6</td>
<td>Yes</td>
</tr>
<tr>
<td>U.K.</td>
<td>British Association of Dermatologists Clinical Standards Unit (2010) (^{16})</td>
<td>Clinicians</td>
<td>14</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Concise Guidelines (2007) (^{13})</td>
<td>Physicians, general practitioners and healthcare professionals (^{a})</td>
<td>7</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>National Institute for Health and Clinical Excellence (2006) (^{10})</td>
<td>Healthcare professionals in primary care (^{a})</td>
<td>7</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Sowerby Centre for Health Informatics at Newcastle (2011) (^{11})</td>
<td>Healthcare professionals in primary care (^{a})</td>
<td>15</td>
<td>Yes</td>
</tr>
</tbody>
</table>

\(^{a}\) Healthcare professionals including nurses, community health care nurses, general practitioners, and/or primary care doctors.

\(^{b}\) Evidence-based review.
<table>
<thead>
<tr>
<th>Country</th>
<th>Guideline</th>
<th>Target audience</th>
<th>Number of risk factors</th>
<th>Differentiation of levels of risk</th>
<th>Evidence base for creation of guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royal College of Surgeons in Ireland (2006)</td>
<td><strong>Clinicians</strong></td>
<td>11</td>
<td>No</td>
<td>1</td>
<td>Consensus recommendation based on review of evidence by committee. Levels of evidence for recommendation provided and grading of recommendations</td>
</tr>
<tr>
<td>Scottish Intercollegiate Guidelines Network (2003)</td>
<td><strong>Healthcare professionals</strong></td>
<td>17</td>
<td>Yes</td>
<td>0</td>
<td>Systematic literature review, critical appraisal and evidence-based summary and level of evidence. Grading of recommendations</td>
</tr>
<tr>
<td>U.S.A. National Comprehensive Cancer Network (2014)</td>
<td><strong>Clinicians and healthcare providers</strong></td>
<td>7</td>
<td>No</td>
<td>3</td>
<td>Systematic literature review, critical appraisal and evidence-based summary and levels of evidence. Grading of recommendations based on level of evidence and consensus b</td>
</tr>
<tr>
<td>American Academy of Dermatology (2011)</td>
<td><strong>Not stated</strong></td>
<td>0</td>
<td>No</td>
<td>3</td>
<td>Systematic literature review, critical appraisal and evidence-based summary and levels of evidence. Grading of recommendations</td>
</tr>
<tr>
<td>National Cancer Institute (2014)</td>
<td><strong>Healthcare professionals</strong></td>
<td>11</td>
<td>No</td>
<td>0</td>
<td>Systematic literature review, critical appraisal and evidence-based summary and levels of evidence. No grading of recommendations</td>
</tr>
<tr>
<td>U.S. Preventive Services Task Force (2009)</td>
<td><strong>Clinicians</strong></td>
<td>6</td>
<td>No</td>
<td>0</td>
<td>Consensus recommendation based on review of evidence by committee. Summary of evidence level, no grading of recommendations b</td>
</tr>
<tr>
<td>American Society of Plastic Surgeons (2007)</td>
<td><strong>Healthcare practitioners</strong></td>
<td>5</td>
<td>No</td>
<td>3</td>
<td>Systematic literature review, critical appraisal and evidence-based summary and levels of evidence. Grading of recommendations</td>
</tr>
</tbody>
</table>

ACNMGRWP Australian Cancer Network Melanoma Guidelines Revision Working Party; EDF, European Dermatology Forum; EADO, European Association of Dermato-Oncology; EORTC, European Organization for Research and Treatment of Cancer; ESMO, European Society for Medical Oncology. aThese guidelines focus mainly on initial assessment and referral (of particular interest to primary care physicians). bLevels of evidence for recommendations were not provided in the guidelines or could not be mapped. References provided in guidelines were assessed by reviewers (C.G.W. and M.D.) using the 2011 Oxford levels of evidence. cGreece is included in ESMO and counted as one of the 20 countries included in the review.

strong family history of melanoma (i.e. 2 to 31-degree relatives with confirmed melanoma) and a personal history of melanoma (Table 2).

While family history was mentioned in 25 guidelines (73%), there were different definitions for this term. Genetic predisposition, usually with regard to CDKN2A mutations, was listed in eight guidelines.13,19,21–23,28–30

Guideline recommendations for screening prior to melanoma diagnosis

Supplementary Table S3 shows a summary of the different countries’ guidelines regarding screening management, applicable to high-risk individuals. Over half (58%) of the guidelines provided recommendations for screening based on...
<table>
<thead>
<tr>
<th>Country and Region</th>
<th>Guideline</th>
<th>High risk</th>
<th>Very high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia and New Zealand</td>
<td>Australian Cancer Network Melanoma Guidelines Revision Working Party (2008)&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Increased number of naevi</td>
<td>&gt; 100 naevi</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinically atypical naevi</td>
<td>&gt; 5 atypical naevi</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Family history (melanoma in one 1st-degree relative)</td>
<td>CDKN2A mutation in a familial setting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fitzpatrick scale skin type I or II</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>History of nonmelanoma skin cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fitzpatrick scale skin type I or II</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Freckles</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Naturally red or blond hair</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>Cancer Care Ontario Program (2007)&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Many (50–100) naevi</td>
<td>&gt; 100 naevi</td>
</tr>
<tr>
<td></td>
<td></td>
<td>One or more atypical (dysplastic) naevi</td>
<td>&gt; 5 atypical naevi</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Family history (melanoma in one 1st-degree relative)</td>
<td>Two or more cases of melanoma in 1st-degree relatives</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fitzpatrick scale skin type I or II</td>
<td>Personal history of skin cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Freckles</td>
<td>Immunosuppressive therapy due to organ transplant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Naturally red or blond hair</td>
<td>&gt; 250 treatments with psoralen plus ultraviolet radiation (PUVA) for psoriasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>History of radiation therapy in childhood</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Dutch Working Group on Melanoma (2013)&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Fitzpatrick scale skin type I or II</td>
<td>Families with high-risk melanoma-associated gene mutations CDKN2A and familial atypical multiple mole melanoma syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Red hair colour</td>
<td>Three or more melanomas, of which two are in 1st-degree relatives or three melanomas of which two melanomas occur in one individual and the affected persons are 1st-degree relatives</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Freckling</td>
<td>Second-degree relatives of CDKN2A-positive families</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Actinic skin damage</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blond hair colour</td>
<td>&gt; 100 naevi</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Large congenital naevus</td>
<td>&gt; 5 atypical naevi</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A medical history of previous skin cancer</td>
<td>Large congenital naevus</td>
</tr>
<tr>
<td>Ukraine</td>
<td>Guidelines Working Group (2014)&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Multiple naevi</td>
<td>Family history of three or more affected family members or history of pancreatic cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Organ transplant recipients</td>
<td>Family history of two or more affected family members with history of multiple primary melanoma or atypical mole phenotype</td>
</tr>
<tr>
<td>U.K.</td>
<td>British Association of Dermatologists Clinical Standards Unit (2010)&lt;sup&gt;16&lt;/sup&gt;</td>
<td>History of melanoma</td>
<td>Congenital naevi &gt; 20 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased number of naevi</td>
<td>Atypical naevus syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinically atypical naevi</td>
<td>Giant congenital naevi &gt; 20 mm or &gt; 5% body surface area</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A family history (at least two cases of melanoma)</td>
<td>A strong family history (at least three cases of melanoma)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunosuppressed due to organ transplant</td>
<td>A strong family history (three cases of melanoma or pancreatic cancer)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>History of a previous melanoma</td>
<td>History of multiple melanomas or pancreatic cancer</td>
</tr>
<tr>
<td></td>
<td>Concise Guidelines (2007)&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Freckles</td>
<td>&gt; 100 naevi</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Red hair or Fitzpatrick scale skin type I or II</td>
<td>Atypical naevi</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Family history (melanoma in one 1st-degree relative)</td>
<td>Two or more cases of melanoma in 1st-degree relatives</td>
</tr>
</tbody>
</table>
Clinical assessment of risk; 11 (32%) provided additional recommendations for those at higher risk and nine provided recommendations including screening intervals for both ‘high risk’ and ‘very high risk’ populations. The use of melanoma risk prediction tools was mentioned in two guidelines but their use was not recommended as they required further validation. One guideline recommended that a patient’s family history be reviewed annually.

There was a general agreement that long-term screening was necessary for individuals at high risk of cutaneous melanoma, particularly where genetic predisposition was identified or suspected because of a strong family history. Twelve guidelines recommended that screening should be based on a prior risk assessment (i.e. an estimate of the risk of developing melanoma demonstrated by the presence of known melanoma risk factors) with intervals defined from 6-monthly to annually, or of ‘regular’ frequency, or ‘lifelong’ duration.

Most guidelines did not discuss genetic testing but for those that did, there was agreement that testing for high-penetration genes should only be carried out in a research setting or after assessment of family history, and where there was provision of adequate support services. Six guidelines mentioned the relevance of a family history of pancreatic cancer to genetic testing or the possible need for surveillance for pancreatic cancer in individuals with CDKN2A mutations. Screening for low-risk genes was currently not recommended.

### Monitoring of naevi

Thirteen guidelines discussed referral of high-risk individuals to a specialist or dermatologist, or clinical management in a specialist clinic. Recommendations regarding monitoring naevi varied from the provision of patient education regarding recognition to the need for 6- to 12-monthly dermoscopic monitoring. Dermoscopy was considered particularly useful for the management of patients with dysplastic naevi, facilitating early diagnosis, improving diagnostic accuracy and reducing the benign: malignant excision ratio of melanocytic lesions.

Most guidelines (70%) discussed the need for specialized training for users of dermoscopy, and generally did not refer to clinician subtypes. Total body photography and sequential digital dermoscopy imaging (SDDI) were the two modalities most frequently mentioned. Total body photography was usually discussed within the context of managing high-risk patients with large numbers of dysplastic naevi, and the early detection of lesions. Short- and long-term monitoring using SDDI was recommended to improve diagnostic accuracy by enhancing the detection of morphological changes over time.

### Table 2 (continued)

<table>
<thead>
<tr>
<th>Country</th>
<th>Guideline</th>
<th>High risk</th>
<th>Very high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sowerby Centre for Health Informatics at Newcastle (2011)</td>
<td>&gt; 50 naevi</td>
<td>&gt; 100 naevi</td>
<td></td>
</tr>
<tr>
<td>Scottish Intercollegiate Guidelines Network (2003)</td>
<td>11–100 naevi &gt; 2 mm</td>
<td>&gt; 100 naevi &gt; 2 mm</td>
<td></td>
</tr>
<tr>
<td>U.S.A.</td>
<td>National Cancer Institute (2014)</td>
<td>Multiple naevi</td>
<td>CDKN2A mutation carriers and 1st-degree family members</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Country</th>
<th>Guideline</th>
<th>High risk</th>
<th>Very high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scotland</td>
<td>Scottish Intercollegiate Guidelines Network (2003)</td>
<td>&gt; 50 naevi</td>
<td>&gt; 100 naevi</td>
</tr>
<tr>
<td></td>
<td>Immunosuppressed</td>
<td>A strong family history (at least three cases of melanoma)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Personal history of melanoma</td>
<td>Multiple atypical naevi</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fitzpatrick scale skin type I or II</td>
<td>Giant congenital naevi &gt; 20 mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11–100 naevi &gt; 2 mm</td>
<td>Four or more atypical naevi</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–3 atypical naevi</td>
<td>Three or more cases of melanoma in 1st-degree relatives</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Family history (melanoma in one 1st-degree relative)</td>
<td>Congenital naevi &gt; 20 cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fitzpatrick scale skin type I or II</td>
<td>History of high sun exposure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>History of melanoma</td>
<td>History of melanoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Actinic lentigines</td>
<td>History of high sun exposure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Light-coloured eyes</td>
<td>History of melanoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Light-coloured skin</td>
<td>History of melanoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple naevi</td>
<td>CDKN2A mutation carriers and 1st-degree family members</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immunosuppressed following organ transplant</td>
<td>Patients with multiple atypical naevi</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Family history</td>
<td>History of excessive sun exposure and previous skin cancer</td>
<td></td>
</tr>
</tbody>
</table>

Risk factors from the nine guidelines that differentiated between ‘high risk’ and ‘very high risk’ individuals.
particularly in lesions lacking dermoscopic features of malignancy. Some guidelines recommended the use of medical photography to document changes in lesion characteristics. Prophylactic removal of naevi was not recommended in any of the guidelines.

Guideline recommendations for follow-up after a melanoma diagnosis

Review of the follow-up section in the guidelines found fewer risk factors for identifying those at high risk of another second or subsequent primary melanoma, compared with screening guidelines which focused on detection of the first primary cutaneous melanoma (Table 1).

Nineteen (55%) guidelines mentioned previous melanoma as a risk factor for a subsequent primary melanoma; in four (12%) guidelines this was the only risk feature mentioned (Table 1). Targeted monitoring was also recommended for those with dysplastic naevi (32%), or a family history (26%). Ten (29%) guidelines contained recommendations that focused on more than one risk factor. Supplementary Table S4 shows a summary of the different countries’ guidelines regarding follow-up after melanoma diagnosis, applicable to high-risk individuals.

Generally, the guidelines that did identify high-risk criteria for follow-up assessment also provided recommendations regarding follow-up intervals for these groups. Five (15%) guidelines contained a general recommendation that follow-up intervals be based on assessment of risk factors for a subsequent primary melanoma. Recommendations for follow-up intervals were usually directed at all patients, however, some recommendations were specifically for high-risk individuals and these advised additional ‘regular’ and/or longer ‘lifelong’ follow-up. There was not always clear differentiation between the risk of a second primary melanoma and the risk of recurrence.

Guideline recommendations for patient education

Supplementary Table S5 shows a summary of the different countries’ guidelines regarding patient education, applicable to high-risk individuals. Recommendations for self-screening or skin self-examination (SSE) were included in 26 (76%) guidelines, and were specifically recommended as part of high-risk management in 13 (38%) guidelines. Advice on SSE, including the signs and symptoms for suspicious lesions and sun protection strategies, was considered pertinent for the management of high-risk individuals both in the context of screening and follow-up. The definition for SSE is not standardized and we identified three main ways of reporting SSE in the guidelines: (i) a statement with no explanation; (ii) a statement that SSE includes an examination of the skin and palpation of lymph nodes sometimes with a recommended interval; (iii) a detailed explanation of the process or a reference or website where information could be obtained.

Recommendations for SSE intervals ranged between monthly, quarterly primary melanoma.32,35,36,40,46 Recommendations for SSE intervals ranged between monthly, quarterly, and 3- to 6-monthly, or were not stated. Recommendations for providing education about sun protection was generally well documented; however, explicit recommendations regarding avoidance of artificial sources of UV light was found in only eight guidelines.

Guideline audience

Most guidelines did not specifically target ‘general practitioners’ or dermatologists’, but defined a broad audience (53%) or ‘clinicians’ (27%) as their target audience, reflecting that melanoma patients are often cared for by multidisciplinary teams of healthcare professionals (Table 1). For seven (21%) the audience was not defined.

Quality of evidence supporting the guideline recommendations

A brief description of the evidence base used to develop each of the guidelines is shown in Table 1. All guideline recommendations were based on a review of the literature and a consensus decision, but not all clearly described their methodology. Of the guidelines using a formal classification system (19 of 34), we found variation in both the grades of evidence (3–8 levels) and strength of recommendations (3–6 levels). Three guidelines provided level of evidence classifications, one a level of evidence and consensus classification, and 15 provided both level of evidence and grade of recommendation. Five (15%) guidelines provided a summary of the level of evidence (but no categories) to support their recommendations.

The level of evidence for specific guideline recommendations aimed at high-risk individuals, graded using the Oxford appraisal tool, is shown in Supplementary Tables S2–S5. There were high levels of evidence supporting assessment of risk factors to identify individuals at high risk of melanoma. There were also high levels of evidence for targeted regular monitoring using dermoscopy and SDDI to increase diagnostic accuracy. There were low levels of evidence for total-body photography. Recommendations for screening intervals and duration of follow-up specifically for high-risk individuals and for SSE were largely consensus-based (level 5 evidence). Sometimes the level of evidence varied depending on the context and terminology used: for example, recommendations regarding dermoscopy ranged from level 1 to 4. If the recommendation referred to the use of dermoscopy to examine dysplastic naevi, then a high level of evidence was applied; but if the recommendation was for 6-monthly screening supported by dermoscopy then a lower level of evidence was applied. In addition, the year in which the guidelines were published meant that the same recommendation could have different levels of evidence. Sometimes similar practices did not have the same level of evidence.
Key recommendations

Table 3 highlights the key recommendations for high-risk individuals that were consistently reported across the different clinical practice guidelines, in relation to risk assessment, management of screening and follow-up. Topics covered include use of dermoscopy, prophylactic removal of naevi, duration of screening and follow-up and patient education.

Discussion

There was agreement between different countries’ clinical practice guidelines that individuals at high risk of melanoma should be identified and screened, and that individuals should receive follow-up to monitor for new or changing lesions after a melanoma diagnosis. There is high-level evidence about melanoma risk factors, but only limited information in

<table>
<thead>
<tr>
<th>Item being described</th>
<th>Oxford level of evidence</th>
<th>Summary of guideline recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk assessment</td>
<td>1–2</td>
<td>Clinicians should be aware of risk factors and groups known to have substantially increased risk of melanoma</td>
</tr>
<tr>
<td></td>
<td>3–4</td>
<td>Alertness for melanoma-suspicious skin lesions should be increased when individuals have a combination of risk features</td>
</tr>
<tr>
<td></td>
<td>3–4</td>
<td>If familial melanoma is suspected, particularly if an individual has large numbers of naevi, referral to a specialist with an interest in melanoma management is advised</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Individuals with melanoma risk factors should be identified by primary healthcare provider and offered surveillance or referred if appropriate to a specialist for surveillance</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Assessment of risk should determine the frequency of surveillance for individuals with increased risk due to a combination of risk factors</td>
</tr>
<tr>
<td>Screening management</td>
<td>1–2</td>
<td>Training and utilization of dermoscopy is recommended for clinicians routinely examining pigmented skin lesions</td>
</tr>
<tr>
<td></td>
<td>1–2</td>
<td>Consider recording dermoscopic images of lesions over time so changes in the lesion can be identified (sequential digital dermoscopy imaging, SDDI)</td>
</tr>
<tr>
<td></td>
<td>3–4</td>
<td>Consider the use of baseline total-body photography in conjunction with dermoscopy as a tool for the early detection of melanoma in patients who are at high risk for developing primary melanoma</td>
</tr>
<tr>
<td></td>
<td>3–4</td>
<td>Individuals with atypical naevi should be advised to have regular follow-up skin examinations at 6- to 12-month intervals</td>
</tr>
<tr>
<td></td>
<td>3–4</td>
<td>High-risk individuals may benefit from annual surveillance by a dermatologist or trained healthcare provider</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Individuals at higher risk should be monitored for life because of risk of malignant change</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>High-risk individuals may benefit from 6-monthly surveillance with a full-body examination supported by total-body photography and sequential dermoscopy as required</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Prophylactic removal of lesions is not recommended in individuals with multiple naevi</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Screening for a mutation should not be done until confirmation of family history and genetic counselling</td>
</tr>
<tr>
<td>Follow-up after melanoma diagnosis</td>
<td>3–4</td>
<td>Patients with pigmented lesions may benefit from dermoscopic imaging or clinical photography</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>More regular follow-up intervals could be recommended where patients have a history of previous melanomas, family history of melanoma or the presence of atypical naevi</td>
</tr>
<tr>
<td>Patient education</td>
<td>3–4</td>
<td>People with high-risk features should not use solariums</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Patients should be educated about self-examination of the skin and lymph nodes, signs and symptoms of melanoma, and photoprotection</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Patients at high risk of recurrence or new primary cancers should be instructed in self-examination and be provided with written and photographic information</td>
</tr>
</tbody>
</table>

© 2014 British Association of Dermatologists
the guidelines for defining ‘high’ and ‘very high’ risk groups and these terms are used inconsistently. This should be addressed in future guidelines in order to inform and streamline screening and follow-up management strategies. There is high-level evidence that dermoscopy improves diagnostic accuracy but it is acknowledged that adequate training is important. The use of total-body photography and SDDI have been shown to be effective in detecting malignant changes and new melanomas in high-risk patients when compared with melanomas diagnosed in the population by other means, and has led to fewer excisions. However, from these studies it is difficult to estimate which diagnostic technique is more beneficial, and studies using control groups have not been performed. Frequent monitoring has been shown to increase patient compliance for follow-up, and further research on the effectiveness of various imaging modalities is ongoing. The use of specialized ‘high-risk clinics’ for follow-up management of high-risk individuals is another model of care currently being evaluated in some countries.

We found generally low levels of evidence supporting recommendations for screening intervals and follow-up duration for high-risk individuals as reported for other cancers. Levels of evidence are important to assist clinicians in evaluating the strength of the recommendations and may be coupled with opinions from experts to place the evidence in context. Randomized trials of clinical management (nontherapeutic interventions) of melanoma are uncommon; therefore, the best-quality evidence is likely to come from prospective observational studies. We were sometimes unable to rate the strength of evidence for the recommendations, when there were only limited references provided in the guidelines, or when the link between the evidence and the recommendation was unclear, a finding that was also reported in a review of stage-specific surveillance practices.

Due to the increasing cost of long-term follow-up care, consideration should be given to strategies for providing patients and their partners with skills for SSE. There is some uncertainty as to whether it is the patient or clinician who is more likely to detect recurrence or a new primary cutaneous melanoma. Patient education for SSE may aid in early detection, but the potential harms and benefits of SSE require further evaluation. Education regarding SSE is a strategy that is particularly pertinent to high-risk groups. Some guidelines reported that not all patients were able to perform SSE, for example due to advanced age, and thus could require more frequent clinical surveillance. Furthermore, regular physician screening may assist in the management of patient anxiety. Other benefits of screening included opportunities for documentation and review, provision of patient information and support, and identification of patient kindreds.

It should be noted that not all guidelines addressed all the topics in this review. For example, some guidelines stated that they focused only on the management of melanoma, thus, risk assessment may not have been discussed. Other guidelines focused on prevention and referral and did not include follow-up recommendations. As we focused on high-risk groups, recommendations for the general population were not necessarily captured in this review.

We suggest some general improvements to the language used in the guidelines, for example: describing risk factors such as ‘many naevi’ or ‘family history’ more precisely to provide clarity around recommendations; quantifying the time period for screening intervals rather than defining as ‘periodic’ or ‘regularly’; and differentiating between follow-up recommendations for another primary melanoma vs. the risk of recurrent disease.

While acknowledging the differences in healthcare systems that will affect the referral and management procedures, clinical practice guidelines for melanoma could be further improved by: (i) providing information about how to identify high-risk individuals; (ii) providing specific recommendations for clinical management of individuals defined as high risk; and (iii) discussing strategies for the most efficient way to monitor high-risk individuals for new primary melanomas. Further research applicable to high-risk individuals includes identifying genetic markers, efficacy of novel diagnostic technologies such as teledermatology, benefits and potential harms of SSE and the ideal techniques, and clinical trials to determine optimal follow-up methods and screening intervals. The examination of the benefits and costs of alternative management strategies will also enhance the quality and practical value of recommendations in future guidelines.

References

Melanoma clinical practice guidelines: a systematic review, C.G. Watts et al. 47


Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

Table S1. The Oxford 2011 Levels of Evidence.

Table S2. Summary of guidelines regarding assessment of level of risk applicable to high-risk individuals.

Table S3. Summary of guidelines applicable to high-risk individuals regarding screening management.

Table S4. Summary of guidelines applicable to high-risk individuals regarding follow-up after melanoma diagnosis.

Table S5. Summary of guidelines applicable to high-risk individuals regarding patient education.
**eTable 1. The Oxford 2011 Levels of Evidence.**

<table>
<thead>
<tr>
<th>Level of evidence*</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N-of -1(^a) randomized trials or systematic review of randomized trials</td>
</tr>
<tr>
<td>2</td>
<td>Randomized trial or observational study with dramatic effect</td>
</tr>
<tr>
<td>3</td>
<td>Non-randomized controlled cohort/follow-up study</td>
</tr>
<tr>
<td>4</td>
<td>Case series, case control studies or historically controlled studies</td>
</tr>
<tr>
<td>5</td>
<td>Mechanism based reasoning</td>
</tr>
</tbody>
</table>

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size. A systematic review is generally better than an individual study.

\(^a\) N-of -1 trial is a type of randomised control trial where alternative treatment regimes are randomly allocated to individual patients and the outcomes compared.

For this review, 5 also applies to consensus based decisions where no level of evidence was provided.
### Table 2. Summary of guidelines regarding assessment of level of risk applicable to high risk individuals.

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Author (Year)</th>
<th>Risk assessment</th>
<th>Levels of Evidence</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| **Australia**  | ACNMGRWP 13(2008) | Clinicians should assess a patient’s future risk of melanoma taking into account known risk factors. Clinicians should identify those who are at high risk and make them aware of their status. | I
|                |                |                 | II, III | IV, V   | 1 |
| **Austria/Italy** | Zalaudek 41(2005) | People who are at greater risk should be identified and encouraged to have regular examination. | I
|                |                |                 |        |        | 3 |
| **Canada**     | Cancer Care Ontario Program 14(2007) | Individuals with melanoma risk factors should be identified by primary health provider and offered appropriate surveillance. Individuals at high risk should be identified by their primary health care provider and followed up by a health care professional with expertise in skin examination. Individuals at higher risk should have clinical assessment of their risk and a surveillance plan. | I
|                |                |                 |        |        | 1, 2, 3 |
| **Netherlands**| Dutch Working Group on Melanoma 25(2013) | Assessment of risk using phenotypic characteristics and family history should be carried on all patients to determine frequency of monitoring. Risk factors for melanoma found to be present should be recorded in the patients file. | I
|                |                |                 |        |        | 1 |
| **Norway**     | Guidelines Working Group 19(2011) | Patients identified with risk factors many naevi, atypical naevi or melanoma in close relatives should be referred to a dermatologist for assessment. | I
|                |                |                 |        |        | 1 |
| **Poland**     | Rutkowski 18(2013) | Medical history should include assessment of the condition of the skin and collect a history about patient’s lifestyle and family history that may determine their risk factors. | I
|                |                |                 |        |        | 1 |
| **South Africa**| Melanoma Advisory Board 23(2004) | High risk individuals should be identified and offered a surveillance program. Consider referral of high risk individuals to a specialist with an interest in melanoma management. Consider referral of family members (if familial melanoma is suspected), particularly those with large numbers of naevi to a specialist with an interest in melanoma management and refer for genetic studies if available. | I
|                |                |                 |        |        | 1, 3 |
| **Spain**      | Mangas 34(2010) | Physicians should identify those a highest risk for melanoma and develop a surveillance plan identifying the type and frequency of screening to monitor their patients. | I
|                |                |                 |        |        | 1, 2, 3 |
| **United Kingdom** | British Association of Dermatology Guidelines 16(2010) | Patients presenting with atypical melanocytic lesions or a large number of naevi should have a complete skin examination and assessment of risk factors. Patients identified as moderately increased risk and at higher risk should be referred to a specialist clinic. | I
|                |                |                 |        |        | 1, 2 |
|                | Concise Guidelines 36(2007) | Clinicians should identify people with higher (10-fold) and lower (approximately 2-to 3-fold) risk. People who are in any of these higher (10-fold) categories should be referred for risk estimation with a dermatologist specialising in naevi and pigmented lesions. Patients with many moles, especially clinically atypical moles merit referral for assessment. People with two or more atypical nevi should be referred for risk estimation to a dermatologist. | I
|                |                |                 |        |        | 1 |
|                | National Institute for | Patients with two or more atypical naevi, and giant congenital naevi where there is suspicion of malignant transformation and who need assessment should be referred for skin cancer health service team assessment and | I
|                |                |                 |        |        | 1, 3 |
| Health and Clinical Excellence\(^{31}\) (2006) | Patients presenting with a lesion where there is suspicion of malignant transformation should be referred for skin cancer health service team assessment and screening.\(^{4}\) | ✓ | 1,3 |
| | Patients in high risk groups should be referred early to a dermatologist for assessment. | ✓ | 1,11 |
| SCHIN\(^{23}\) (2011) | If patients are at higher risk for melanoma they should be referred for risk estimation. | ✓ | 1 |
| Scottish Intercollegiate Guidelines Network\(^{29}\) (2003) | Health care professionals should be aware of risk factors for melanoma. Patients with suspicious pigmented lesions should be referred to a specialist clinic in a time commensurate with physicians concern.\(^{2}\) | ✓ | 1,2,3,4 |
| USA | American Society of Plastic Surgeons\(^{33}\) (2009) | Patient’s presenting with unusual cutaneous lesions should undergo a comprehensive medical history and physical examination to assess the possibility of melanoma. The patient history should focus on clinical characteristics associated with a higher risk for melanoma.\(^{a}\) | ✓ | 1 |
| | National Comprehensive Cancer Network\(^{39}\) (2013) | Preliminary workup of patient presenting with dysplastic naevi or melanoma should include detailed personal and family history, assessment of melanoma related risk factors, including any history of removal of melanoma or dysplastic naevi, family history of melanoma, presence of atypical naevi and dysplastic naevi. | ✓ | 1 |
| | National Cancer Institute\(^{25}\) (2012) | Patients with a family history of melanoma should be asked to provide information regarding family history of melanoma and other cancers to detect the presence of familial melanoma. Age at diagnosis and confirmation of pathology should be sought. | ✓ | 1 |
| | US Preventive Service Network.\(^{58}\) (2009) | Clinicians should make an assessment of risk and remain alert for skin lesions.\(^{7}\) | ✓ | 3 |
| | | Clinicians should be aware of risk factors and groups known to have substantially increased risk of melanoma.\(^{a}\) | ✓ | 3 |
### eTable 3. Summary of guidelines applicable to high risk individuals regarding screening management.

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Author$^a$ (Year)</th>
<th>Screening management</th>
<th>Levels of Evidence</th>
<th>Outcome$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Australian Cancer Network Melanoma Group Revision Working Party$^{13}$</td>
<td>High risk individuals may benefit from regular surveillance by a clinician</td>
<td>✓</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High risk individuals may benefit from six monthly surveillance with a full body examination supported by total photography and dermoscopy as required</td>
<td>✓, ✓</td>
<td>2,3,6,7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Training and utilisation of dermoscopy is recommended for clinicians routinely examining pigmented skin lesions</td>
<td>✓</td>
<td>3,7,8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider the use of sequential digital dermoscopy imaging to detect melanomas that lack dermoscopic features of melanoma</td>
<td>✓</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider the use of baseline total body photography as a tool for the early detection of melanoma in patients who are at high risk for developing primary melanoma</td>
<td>✓, ✓</td>
<td>3,7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prophylactic removal of lesions are not recommended in individuals with multiple naevi</td>
<td>✓</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For some patients with lentigo maligna, observation for change using macroscopic or dermoscopic photography and measurement is an acceptable alternative to immediate excision</td>
<td>✓, ✓</td>
<td>6,7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Screening for a mutation should not be done until confirmation of family history and genetic counseling</td>
<td>✓</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Routine removal of small and medium size congenital melanocytic naevi is not recommended</td>
<td>✓</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biopsy or removal of small to medium congenital melanocytic naevi showing suspicious features should be undertaken</td>
<td>✓</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biopsy or removal of large congenital melanocytic naevi may be appropriate where suspicious features are evident</td>
<td>✓</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lifetime surveillance of patients with large congenital melanocytic naevi is recommended. This could include baseline photography and three monthly evaluations for the first year of life, followed by six monthly evaluations for the next three years and then yearly</td>
<td>✓</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MRI of the brain should be undertaken in patients with large congenital naevi in an axial distribution and those with multiple large scattered lesions</td>
<td>✓</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Screening for a mutation such as CDKN2A gene be contemplated only after a thorough clinical risk assessment, confirmation of a strong family history and appropriate genetic counselling.</td>
<td>✓</td>
<td>1</td>
</tr>
<tr>
<td>Canada</td>
<td>BC Cancer Agency$^{15}$ (2013)</td>
<td>Individuals with a strong family history (2 or more first degree relatives with melanoma), who may carry p16 (INK4A) germline mutation, predisposing to disease, history of previous melanoma and those with atypical nevus syndrome (formerly dysplastic naevus syndrome) should have regular (for example annual) surveillance, ideally by a dermatologist.</td>
<td>✓</td>
<td>3,4,5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Individuals with atypical naevi should be advised to have regular follow-up skin examinations at 6 to 12 month intervals</td>
<td>✓</td>
<td>2,3,5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prophylactic removal of lesions are not recommended in individuals with an increased number of melanocytic naevi</td>
<td>✓</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>It is recommended that large congenital melanocytic naevi be excised as early as possible.</td>
<td>✓</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients who have had a congenital melanocytic naevi excised should be kept under surveillance and reviewed at 6-12 month intervals</td>
<td>✓</td>
<td>3</td>
</tr>
<tr>
<td>Source</td>
<td>Recommendation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer Care Ontario Program</td>
<td>Patients with a history of excised congenital melanocytic naevi should be kept</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2007)</td>
<td>under surveillance. Follow-up examinations at 6 to 12 month intervals are</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>generally recommended.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Individuals at very high risk should be offered total body skin examination by</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>a dermatologist or a trained health care provider with expertise in skin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>examination on a yearly basis.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Individuals who have undergone organ transplant and are on chronic immunosuppressant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>therapy should be reviewed by a dermatologist or someone with dermatological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>expertise regularly.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Individuals at high risk should have annual surveillance by a health care provider</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>trained in screening for skin cancers.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total body photographs are useful to assist with monitoring.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canadian Dermatology</td>
<td>Physical examination, digital and regular photography and dermoscopy are</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Association (2009)</td>
<td>important in establishing a diagnosis of melanoma.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dermoscopy requires formal training.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>In high risk patients, mainly in the case of patients with atypical mole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>syndrome, the detection of changes in the lesions or newly appearing lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>by follow-up examination with digital dermoscopy and total body photography is</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>also helpful.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dermoscopy should be used to clarify the differential diagnosis of pigmented</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>lesions. In order to apply this technique, training and expertise are required.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria /Italy</td>
<td>People who are at greater risk should be encouraged to have regular examination.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>People with xeroderma pigmentosum are high risk and should have special</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>follow-up.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>People with numerous naevi or the syndrome of hereditary dysplastic naevi,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>surveillance should be life-long.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>People with numerous naevi prophylactic removal of lesions is not justified as</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>the risk of melanoma transformation is too low.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>People with at risk should be encouraged to have regular examination.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>People with familial melanoma should be monitored using dermoscopy.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Use of dermoscopy requires special training.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>If change occurs in large congenital naevus biopsy is appropriate.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>People with xeroderma pigmentosum are high risk and should have special</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>follow-up.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High risk patients should be screened in dermatology clinics where dermoscopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>and photography is used.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>If patients have numerous naevi or the syndrome of hereditary dysplastic naevi,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>surveillance should be life-long.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>In patients with numerous naevi prophylactic removal of lesions is not justified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>as the risk of melanoma transformation is too low.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>High risk patients should have dermatologist screening annually.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Use of dermoscopy requires special training.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>For the diagnosis of pigmented skin lesions, dermatologists shall offer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>dermoscopy and be trained in the field of dermoscopy.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>During the course of observation, sequential digital dermoscopy can improve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>early recognition of melanomas that lack specific dermoscopic criteria of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>malignancy.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Whole body photography represents one possibility for early recognition of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>melanoma in individuals at risk.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>People with dysplastic naevi should be monitored using dermoscopy.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Regular monitoring should also be considered for individuals with increased risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>or loading due to a combination of risk factors.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pigmented skin lesions should be monitored, if possible using dermoscopy imaging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>Dermatoscopy should have a permanent role in the clinical diagnosis of pigmented</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>skin abnormalities.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>It is important the users of dermoscopy be trained in this technique before</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>clinical application.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>It is recommended to start screening patients from families where familial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>melanoma has been confirmed.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td>Guidelines Working Group(^\text{19}) (2011)</td>
<td>People with family history (known genetic mutation) and atypical/dysplastic nevus syndrome should have continuous dermoscopy monitoring by a dermatologist annually.</td>
<td>✓</td>
<td>3,4,7</td>
</tr>
<tr>
<td>Norway</td>
<td>Guidelines Working Group(^\text{19}) (2011)</td>
<td>People with a family history of melanoma or in higher risk groups in terms of skin type should be regularly screened by a dermatologist or clinician.</td>
<td>✓</td>
<td>3,4</td>
</tr>
<tr>
<td>Norway</td>
<td>Guidelines Working Group(^\text{19}) (2011)</td>
<td>Patients with large congenital naevi (&gt;20cm) are at increased risk for melanoma, and should be monitored regularly.</td>
<td>✓</td>
<td>3,4</td>
</tr>
<tr>
<td>Norway</td>
<td>Guidelines Working Group(^\text{19}) (2011)</td>
<td>Patients from families with a total of at least 3 melanomas in close family relatives, be referred to a medical geneticist.</td>
<td>✓</td>
<td>3,11</td>
</tr>
<tr>
<td>Norway</td>
<td>Guidelines Working Group(^\text{19}) (2011)</td>
<td>Patients from families with a total of at least 3 melanomas in close family relatives, should be offered regular skin examination checks by a general practitioner or dermatologist.</td>
<td>✓</td>
<td>2,3,4</td>
</tr>
<tr>
<td>Norway</td>
<td>Guidelines Working Group(^\text{19}) (2011)</td>
<td>Patients with atypical naevi or family history of melanoma should be under the care of a dermatologist proficient in using dermoscopy.</td>
<td>✓</td>
<td>3,4,7</td>
</tr>
<tr>
<td>Norway</td>
<td>Guidelines Working Group(^\text{19}) (2011)</td>
<td>Excision of atypical naevi is not recommended, unless there is suspicion of malignancy.</td>
<td>✓</td>
<td>6</td>
</tr>
<tr>
<td>Norway</td>
<td>Guidelines Working Group(^\text{19}) (2011)</td>
<td>For patients at high risk, whole body photography can be helpful for following development of nevi, particularly in detecting new lesions early.</td>
<td>✓</td>
<td>3,7</td>
</tr>
<tr>
<td>Norway</td>
<td>Guidelines Working Group(^\text{19}) (2011)</td>
<td>Genetic testing should only be offered to patients where familial melanoma is suspected and at a specialised centre</td>
<td>✓</td>
<td>3,11</td>
</tr>
<tr>
<td>Norway</td>
<td>Guidelines Working Group(^\text{19}) (2011)</td>
<td>People who have had more than one melanoma should be referred to a specialised centre</td>
<td>✓</td>
<td>3,4</td>
</tr>
<tr>
<td>Norway</td>
<td>Guidelines Working Group(^\text{19}) (2011)</td>
<td>Follow-up for newborns with large congenital naevi should consist of an MRI within the first 6 months of life Follow-up should depend on size and number of lesions and annual monitoring may be necessary.</td>
<td>✓</td>
<td>3</td>
</tr>
<tr>
<td>Norway</td>
<td>Guidelines Working Group(^\text{19}) (2011)</td>
<td>Follow-up for individuals with congenital naevi should depend on size and number of lesions and annual monitoring may be necessary.</td>
<td>✓</td>
<td>3</td>
</tr>
<tr>
<td>Norway</td>
<td>Guidelines Working Group(^\text{19}) (2011)</td>
<td>Users of dermoscopy should be trained.</td>
<td>✓</td>
<td>7</td>
</tr>
<tr>
<td>New Zealand</td>
<td>NZ Guidelines Group(^\text{27}) (2009)</td>
<td>Clinical diagnosis of melanoma may be enhanced where clinicians are trained in and use dermoscopy in</td>
<td>✓</td>
<td>7,8</td>
</tr>
<tr>
<td>New Zealand</td>
<td>NZ Guidelines Group(^\text{27}) (2009)</td>
<td>from 12 years for 1(^{st}) degree relatives and 20 years for 2(^{nd}) degree relatives.</td>
<td>✓</td>
<td>3,11</td>
</tr>
<tr>
<td>New Zealand</td>
<td>NZ Guidelines Group(^\text{27}) (2009)</td>
<td>Regular monitoring at 6-12 month intervals should be considered for individuals with markedly increased risk of melanoma (confirmed familial risk) beginning at age 12.</td>
<td>✓</td>
<td>3,11</td>
</tr>
<tr>
<td>New Zealand</td>
<td>NZ Guidelines Group(^\text{27}) (2009)</td>
<td>It is recommended to refer melanoma patients for whom the diagnosis of familial melanoma/FAMM syndrome is being considered to a clinical genetic centre.</td>
<td>✓</td>
<td>3,11</td>
</tr>
<tr>
<td>New Zealand</td>
<td>NZ Guidelines Group(^\text{27}) (2009)</td>
<td>It is recommended for CDKN2A mutation carriers from the age of 45 years to be referred to a gastro-enterohepatolgy specialist in one of the centres in which pancreatic examination is taking place within a research context.</td>
<td>✓</td>
<td>1,11</td>
</tr>
<tr>
<td>New Zealand</td>
<td>NZ Guidelines Group(^\text{27}) (2009)</td>
<td>Alertness for melanoma in suspicious skin lesions should be increased when individuals have a combination of risk factors.</td>
<td>✓</td>
<td>1,3</td>
</tr>
<tr>
<td>New Zealand</td>
<td>NZ Guidelines Group(^\text{27}) (2009)</td>
<td>Dermoscopy should be used to assist in assessment of pigmented skin lesions. It is important the user is trained.</td>
<td>✓</td>
<td>7,8</td>
</tr>
<tr>
<td>New Zealand</td>
<td>NZ Guidelines Group(^\text{27}) (2009)</td>
<td>It is not recommended to perform routine follow-up of congenital nevi (CN) with a diameter of 20 cm or smaller. However it is recommended that parents are instructed to return for consultation if there are any changes of small- middle size CN (&lt;20cm) in children.</td>
<td>✓</td>
<td>*</td>
</tr>
<tr>
<td>New Zealand</td>
<td>NZ Guidelines Group(^\text{27}) (2009)</td>
<td>As soon as possible after the birth of a baby with a large CN, a multidisciplinary team in a paediatric surgery centre as soon after birth as possible is desirable, in relation to the option of neonatal curettage. Regular follow-up with inspection and palpation is advisable.</td>
<td>✓</td>
<td>3</td>
</tr>
</tbody>
</table>

\(^\text{19}\) Guidelines Working Group (2011) - Norway
\(^\text{27}\) NZ Guidelines Group (2009) - New Zealand
<table>
<thead>
<tr>
<th>Country</th>
<th>Reference</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poland</td>
<td>Rutkowski (2013)</td>
<td>Excision of atypical naevi is not recommended unless there is suspicion of malignancy.</td>
</tr>
<tr>
<td>South Africa</td>
<td>Melanoma Advisory Board (2004)</td>
<td>Digital monitoring is useful to monitor high risk patients aiding in visualization and documentation of lesions.</td>
</tr>
<tr>
<td>Spain</td>
<td>Mangas (2010)</td>
<td>Regular dermoscopic monitoring by a dermatologist of individuals at high risk for developing malignant melanoma is generally recommended.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The dermoscope is also useful for monitoring multiple pigmented lesions where photography of dermoscopic images provide a record of change.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long term follow-up is recommended for people with giant congenital nevus, who have had organ transplants, or large numbers of naevi which may be clinically atypical.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Individuals at greatly increased risk should be monitored for life because of the risk of malignant change.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Close-up and distant photography may be an effective adjunct to detecting early melanoma in either high risk groups.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider referral to a geneticist for patients who have atypical naevi.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider referral to clinical geneticist or specialized dermatology services for genetic counseling where there is a family history of melanoma with three or more reported cases of melanoma or pancreatic cancer.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prophylactic excision of small congenital naevi is not recommended.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients with giant congenital naevi are at increased risk of melanoma and require long term follow up.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excision biopsy of suspicious areas in large congenital naevi may be necessary but requires expert histological review.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Photography can be useful for follow-up of patients who have atypical naevi.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline photography is a useful aid to monitoring moles.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atypical moles are those that must be monitored but the absolute risk of melanoma is so low that</td>
</tr>
<tr>
<td>Organization</td>
<td>Statement</td>
<td>References</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
<td>------------</td>
</tr>
<tr>
<td>National Institute for Health and Clinical Excellence</td>
<td>Prophylactic excision is not justified.</td>
<td>3,4</td>
</tr>
<tr>
<td></td>
<td>Patients from high risk groups or at high risk of skin cancer should be referred to a dermatologist for assessment, active treatment and have annual check-ups.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Use of dermoscopy should be utilized but requires training.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Medical photography should be utilized for surveillance of patients with atypical naevi.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>High risk patients should have 6 monthly check-ups once skin lesions develop.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Patients with evidence of genetic predisposition to melanoma should be referred to clinical genetic services or a specialist dermatology service.</td>
<td>✓</td>
</tr>
<tr>
<td>Royal College of Surgeons</td>
<td>Photography may be a useful adjunct to detecting early melanomas in high risk groups.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Prophylactic excision of small naevi is not recommended.</td>
<td>✓</td>
</tr>
<tr>
<td>Scottish Intercollegiate Guidelines Network</td>
<td>Genetic testing in familial or sporadic melanoma is not appropriate and should only be undertaken in the context of appropriate research studies.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Clinicians using hand held dermoscopy should be appropriately trained.</td>
<td>✓</td>
</tr>
<tr>
<td>SCHIN</td>
<td>The dermatoscope should only be used by professionals who have had adequate training in its use.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Patients who are immunocompromised or have a genetic predisposition may need more investigations, more intensive earlier follow-up and specific supportive care.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Long term follow-up usually with a dermatologist is recommended for people at higher risk of melanoma</td>
<td>✓</td>
</tr>
<tr>
<td>USA</td>
<td>Lifetime surveillance (3-12 months) is recommended for patients if there are additional factors that may influence follow-up interval (family history of melanoma, clinically atypical naevi).</td>
<td>✓</td>
</tr>
<tr>
<td>American Academy of Dermatology</td>
<td>Individuals with high risk features should undergo professional evaluation at least once a year.</td>
<td>✓</td>
</tr>
<tr>
<td>American Society of Plastic Surgeons</td>
<td>For patients with atypical naevi, dermoscopy should be utilized with total body photography.</td>
<td>✓</td>
</tr>
<tr>
<td>National Comprehensive Cancer Network</td>
<td>Patients with a personal history of melanoma or dysplastic naevi should have annual review and their family histories should be updated regularly.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Members of melanoma prone families should have regular examination of the skin by a practitioner experienced in the evaluation of pigmented lesions.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Observation of lesions may be aided by techniques such as full body photography and dermoscopy.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Regular dermoscopic monitoring of individuals at high risk is advised.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Close dermatologic follow-up of individuals from families where CDKN2A mutation has been identified is warranted, regardless of genetic testing result.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>For patients with atypical naevi, dermoscopy should be utilized with total body photography.</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Biopsies of lesions for high-risk population should be performed using the same criteria as in the general population. Prophylactic removal of naevi is not recommended.</td>
<td>✓</td>
</tr>
<tr>
<td>National Cancer Institute</td>
<td>While genetic testing to confirm germline mutations in CDKN2A may assist with management, members</td>
<td>✓</td>
</tr>
</tbody>
</table>
Recommendation for general population

| 1. Identification of high risk groups. | 2. Increased monitoring. | 3. Early detection of melanoma. | 4. Improved prognosis. | 5. Decreased morbidity. | 6. Reduction in unnecessary excisions. | 7. Improved diagnostic accuracy. | 8. Improved sensitivity and specificity. | 9. Improve risk reducing behaviour associated with melanoma. | 10. Improve patient’s ability to detect changes on the skin. | 11. Improve patient support (psychological outcomes). |

Pancreatic cancer should be considered for CDKN2A mutation carriers only if there is a family history of pancreatic cancer and within the context of a clinical trial.

---

*Abbreviations: ACNMGRW Australian Cancer Network Melanoma Guidelines Revision Working Party, DDG and DeCOG, European Dermatology Forum, European Association of Dermato-Oncology and European Organization for Research and Treatment of Cancer, SCHIN Sowerby Centre for Health Informatics at Newcastle*

*Outcome of interest.*

1. Identification of high risk groups.
2. Increased monitoring.
3. Early detection of melanoma.
4. Improved prognosis.
5. Decreased morbidity.
6. Reduction in unnecessary excisions.
7. Improved diagnostic accuracy.
8. Improved sensitivity and specificity.
10. Improve patient’s ability to detect changes on the skin.
11. Improve patient support (psychological outcomes).

*Outcome not provided*
Table 4. Summary of guidelines applicable to high risk individuals regarding follow-up after melanoma diagnosis.

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Author <em>(Year)</em></th>
<th>Follow-up after melanoma diagnosis</th>
<th>Levels of Evidence</th>
<th>Outcome&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>ACNMGRWP&lt;sup&gt;11&lt;/sup&gt;</td>
<td>More regular follow-up intervals may be warranted for patients with family history of melanoma or the presence of atypical naevi.</td>
<td>✓</td>
<td>2,3</td>
</tr>
<tr>
<td>Austria/Italy</td>
<td>Zalaudek&lt;sup&gt;24&lt;/sup&gt; (2005)</td>
<td>All patients should have life-long surveillance at regular intervals.&lt;sup&gt;a&lt;/sup&gt;</td>
<td>✓</td>
<td>3,5</td>
</tr>
<tr>
<td>Brazil</td>
<td>Brazilian Society of Dermatology&lt;sup&gt;24&lt;/sup&gt; (2012)</td>
<td>More regular follow-up intervals would be recommended where patients have a history of previous melanomas, family history of melanoma or the presence of atypical naevi.</td>
<td>✓</td>
<td>1,3,4,5</td>
</tr>
<tr>
<td>Canada</td>
<td>BC Cancer Agency&lt;sup&gt;12&lt;/sup&gt; (2013)</td>
<td>Patients with a history of atypical mole or strong family history of melanoma may require more frequent follow-up.</td>
<td>✓</td>
<td>2,3</td>
</tr>
<tr>
<td></td>
<td>Cancer Care Ontario Program&lt;sup&gt;12&lt;/sup&gt; (2007)</td>
<td>Individuals at very high risk should be referred for follow-up in specialist care.</td>
<td>✓</td>
<td>2,3,5</td>
</tr>
<tr>
<td></td>
<td>Alberta Health Service&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Follow-up with regard to depth of lesion for first three years and annual skin examination for life.&lt;sup&gt;a&lt;/sup&gt;</td>
<td>✓</td>
<td>3,11</td>
</tr>
<tr>
<td></td>
<td>Canadian Dermatology Association&lt;sup&gt;14&lt;/sup&gt; (2009)</td>
<td>Follow-up examinations for patient’s lifetime. An annual complete skin examination by a dermatologist is recommended.&lt;sup&gt;a&lt;/sup&gt;</td>
<td>✓</td>
<td>3</td>
</tr>
<tr>
<td>Finland</td>
<td>Finnish Medical Society&lt;sup&gt;20&lt;/sup&gt; (2012)</td>
<td>There should be assessment of risk for new primary melanomas.&lt;sup&gt;a&lt;/sup&gt;</td>
<td>✓</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If patients have high risk features, numerous naevi or dysplastic nevus syndrome, or hereditary melanoma, follow-up should be in a dermatology unit. High risk patients should be followed up in dermatology clinics.</td>
<td>✓</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High quality photos facilitate follow-up for patients with high risk features.</td>
<td>✓</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If patients have numerous naevi or dysplastic nevus syndrome, or hereditary melanoma, follow-up should be lifelong.</td>
<td>✓</td>
<td>3,11</td>
</tr>
<tr>
<td>France</td>
<td>French Society Dermatology&lt;sup&gt;41&lt;/sup&gt; (2007)</td>
<td>Patients should be followed up according to the stage of melanoma for the first five years and after that annually for life.&lt;sup&gt;a&lt;/sup&gt;</td>
<td>✓</td>
<td>3,4</td>
</tr>
<tr>
<td></td>
<td>National Institute of Cancer&lt;sup&gt;26&lt;/sup&gt; (2010)</td>
<td>Patients should be monitored once a year for life.&lt;sup&gt;a&lt;/sup&gt;</td>
<td>✓</td>
<td>3</td>
</tr>
<tr>
<td>Germany</td>
<td>DDG and DeCOG (2013)&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Stage-adapted follow-up of melanoma patients should extend over a period of ten years.&lt;sup&gt;a&lt;/sup&gt;</td>
<td>✓</td>
<td>3,11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High risk patients (Dysplastic Nevus Syndrome, familial melanoma) should be followed up annually by a specialist for life.</td>
<td>✓</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After ten years measures should be limited to regular skin self examination&lt;sup&gt;a&lt;/sup&gt;</td>
<td>✓</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients with individual risk factors(dysplastic nevus syndrome, family history) should have access to long term dermatologic exams in addition to regular follow-up.</td>
<td>✓</td>
<td>3</td>
</tr>
<tr>
<td>Italy</td>
<td>Italian Groups Dermatology (GIDO) and Oncology and Multidiscipline of melanoma (GIPMe)&lt;sup&gt;24&lt;/sup&gt; (2007)</td>
<td>More regular follow-up intervals could be considered for patients with disseminated atypical naevi.</td>
<td>✓</td>
<td>2,3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Identify patients with pigmented lesions who may require monitoring.&lt;sup&gt;a&lt;/sup&gt;</td>
<td>✓</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients with pigmented lesions may benefit from dermoscopic imaging.&lt;sup&gt;a&lt;/sup&gt;</td>
<td>✓</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients should be followed up according to the stage of melanoma for the first ten years and after that annually for life.&lt;sup&gt;a&lt;/sup&gt;</td>
<td>✓</td>
<td>3</td>
</tr>
<tr>
<td>Norway</td>
<td>Guidelines Working Group&lt;sup&gt;14&lt;/sup&gt; (2011)</td>
<td>Presence of atypical naevi and patients with family history of melanoma may indicate a need for closer follow-up.</td>
<td>✓</td>
<td>3,4</td>
</tr>
<tr>
<td>Country</td>
<td>Reference</td>
<td>Recommendation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>------------</td>
<td>----------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>Mangas (2010)</td>
<td>Patients with a family history of melanoma or who have clinically atypical naevi should have lifelong surveillance.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>Dummer (2012)</td>
<td>Lifelong surveillance is recommended.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>National Institute for Health and Clinical Excellence (2006)</td>
<td>Patients at high risk of recurrence or new primary cancers should normally be followed up in a hospital.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SCHIN (2011)</td>
<td>If patients are at higher risk for melanoma they should be referred for follow-up.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Royal College of Surgeons (2009)</td>
<td>For patients with multiple atypical naevi, clinical photography may be helpful in follow-up.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>American Academy of Dermatology (2011)</td>
<td>At least annual follow-up, ranging from every 3-12 months based on risk for recurrence, follow-up interval may also be influenced by history of multiple primary melanomas, presence of clinically atypical naevi or family history of melanoma.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>American Society of Plastic Surgeons (2009)</td>
<td>Patients with poor prognostic indicators or history of multiple melanomas, presence of clinically atypical naevi or family history of melanoma require more frequent follow-up and should have full skin assessment every 3 months for 2-3 years following a melanoma.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>National Comprehensive Cancer Network (2013)</td>
<td>Follow-up schedules is influenced by risk of recurrence and other risk factors, previous primary melanoma, family history of melanoma, other factors such as presence of atypical moles/dysplastic naevi, and patient physician concern.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Note**: Recommendation for general population

Abbreviations: ACNMGRW Australian Cancer Network Melanoma Guidelines Revision Working Party, DDG and DeCOG, European Dermatology Forum, European Association of Dermato-Oncology and European Organization for Research and Treatment of Cancer; SCHIN Sowerby Centre for Health Informatics at Newcastle

Outcome of interest:
1. Identification of high risk groups.
2. Increased monitoring.
3. Early detection of melanoma.
4. Improved prognosis.
5. Decreased morbidity.
6. Reduction in unnecessary excisions.
7. Improved diagnostic accuracy.
8. Improved sensitivity and sensitivity.
10. Improve patient’s ability to detect changes on the skin.
11. Improve patient support (psychological outcomes).
*Outcome not provided
1 Excluding guidelines about tumor thickness and factors for recurrence
# Table 5. Summary of guidelines applicable to high risk individuals regarding patient education.

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Author(^b)(Year)</th>
<th>Patient education</th>
<th>Levels of Evidence</th>
<th>Outcome(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Australia/New Zealand</strong></td>
<td>ACNMGRWP(^d) (2013)</td>
<td>Individuals at high risk and their partners should be educated to recognize and document lesions suspicious of melanoma. Individuals at high risk should self-screen in between review appointments.</td>
<td></td>
<td>✓ 10</td>
</tr>
<tr>
<td><strong>Austria/ Italy</strong></td>
<td>Zalaudek(^d) (2005)</td>
<td>People with risk factors should be made aware of their increased risk and encouraged to make regular examinations. People with Type I skin should not use sunbeds.</td>
<td></td>
<td>✓ 10</td>
</tr>
<tr>
<td><strong>Brazil</strong></td>
<td>Brazilian Society of Dermatology(^d) (2012)</td>
<td>Patients should be educated about self-examination of the skin and lymph nodes, signs and symptoms of melanoma and photo protection.(^a)</td>
<td></td>
<td>✓ 9,10</td>
</tr>
<tr>
<td><strong>Canada</strong></td>
<td>BC Cancer Agency(^d) (2013)</td>
<td>Individuals with increased number of melanocytic naevi or atypical naevi should be advised to avoid excessive sun exposure.</td>
<td></td>
<td>✓ 9</td>
</tr>
<tr>
<td></td>
<td>Cancer Care Ontario Program(^d) (2007)</td>
<td>All patients at risk should be taught how to examine their own skin and should do so once a month.</td>
<td></td>
<td>✓ 3,10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Individuals at very high risk should be counseled about skin self-examination and skin cancer prevention by a health care provider.</td>
<td></td>
<td>✓ 9,10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Individuals at high risk should be counseled about skin self-examination and skin cancer prevention by a health care provider.</td>
<td></td>
<td>✓ 9,10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Individuals at higher risk should be referred for education on self-examination.</td>
<td></td>
<td>✓ 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Individuals at higher risk should be advised on prevention of skin cancer and encouraged to perform monthly self-examination and advised on the signs and symptoms of suspicious lesions.</td>
<td></td>
<td>✓ 9,10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Individuals at increased risk should be advised on prevention of skin cancer and encouraged to perform monthly self-examination and advised on the signs and symptoms of suspicious lesions.</td>
<td></td>
<td>✓ 9,10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin self-examination techniques can be enhanced by using photographs. It is advisable for these to be taken professionally but if this is not possible a family member should be advised on how to take these photos. Photographs should be referred to monthly.</td>
<td></td>
<td>✓ 10</td>
</tr>
<tr>
<td></td>
<td>Alberta Health Service(^d) (2011)</td>
<td>Educate patient on monthly skin self-examination if in-situ melanoma.(^a)</td>
<td></td>
<td>✓ 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Educate patient on monthly skin self-examination and lymph node examination if invasive melanoma.(^a)</td>
<td></td>
<td>✓ 3,10</td>
</tr>
<tr>
<td></td>
<td>Canadian Dermatology Association(^d) (2009)</td>
<td>Educate patient on monthly skin self-examination.</td>
<td></td>
<td>✓ 3,10</td>
</tr>
<tr>
<td><strong>Europe</strong></td>
<td>European Society for Medical Oncology(^d) (2012)</td>
<td>Melanoma patients should be instructed in sun protection and in lifelong regular self-examinations of the skin and peripheral lymph nodes.(^a)</td>
<td></td>
<td>✓ 9,10</td>
</tr>
<tr>
<td></td>
<td>EDF,EADO,EORTC(^d) (2012)</td>
<td>Provide education on prevention and self-examination</td>
<td></td>
<td>✓ 9,10</td>
</tr>
<tr>
<td><strong>Finland</strong></td>
<td>Finnish Medical Society(^d) (2012)</td>
<td>High risk groups should be shown how to examine their skin and to seek medical attention if there are any skin changes.</td>
<td></td>
<td>✓ 3,10,11</td>
</tr>
<tr>
<td>Country</td>
<td>Source</td>
<td>Advice</td>
<td>Reference(s)</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>National Institute of Cancer (2010)</td>
<td>Individuals with Type I skin should be advised to not use sunbeds.</td>
<td>✓ 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>French Society Dermatology (2007)</td>
<td>If under 30 years of age with a melanoma history, advice should be given to avoid the sun and avoid solarium because of the risk of second primary.</td>
<td>✓ 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>If under 30 years of age with a melanoma history, patients under 30 years at greater risk and should receive education about sun-protection</td>
<td>✓ 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients should be educated about self-screening, and sun protection. Verbal information should be supplemented by written information.</td>
<td>✓ 9,10</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>DDG and DeCOG (2013)</td>
<td>Patients should receive instruction on self-examination to detect a new melanoma or recognize a recurrence themselves.</td>
<td>✓ 10,11</td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>Dutch Working Group on Melanoma (2015)</td>
<td>If an elevated risk in patients is detected, patients should be informed of this and provided with information and receive instruction on self-examination.</td>
<td>✓ 10,11</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients should be advised that sunburn should be avoided.</td>
<td>✓ 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>The use of tanning beds by people under 35 years should be advised against.</td>
<td>✓ 9</td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td>Guidelines Working Group (2011)</td>
<td>People with family history (known genetic mutation) and atypical/dysplastic nevus syndrome should receive education about sun protection.</td>
<td>✓ 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients should receive instruction on how to perform self-examination.</td>
<td>✓ 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>People with a family history of melanoma or in higher risk groups in terms of skin type should receive advice about sun protection and self skin examination.</td>
<td>✓ 9,10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>People with high risk features should not use solariums.</td>
<td>✓ 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Persons under 18 years should not use solariums.</td>
<td>✓ 9</td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>Melanoma Advisory Board (2013)</td>
<td>High risk individuals should be advised on specific skin changes which suggest melanoma and be encouraged to undertake self-examination and advised regarding sun protection.</td>
<td>✓ 9,10</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>Mangas (2010)</td>
<td>All patients should receive instruction on how to carry out monthly self-examination and implement effective photo-protection.</td>
<td>✓ 9,10</td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>Dummer (2012)</td>
<td>All patients should receive instruction in effective photo-protection and on life-long regular self-examination of the skin.</td>
<td>✓ 9,10</td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>British Association of Dermatology Guidelines (2010)</td>
<td>Individuals at increased risk and should be counseled about their risk and taught how to self-examine for changing naevi</td>
<td>✓ 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Concise Guidelines (2007)</td>
<td>Individuals at greatly and moderately increased risk and should be advised on changes that suggest melanoma and encouraged to undertake monthly skin self-examination</td>
<td>✓ 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Target advice about sun avoidance at those most at risk.</td>
<td>✓ 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>People who are in any of these higher (10-fold) categories should be referred for education directed toward self examination with a dermatologist specialising in naevi and pigmented lesions.</td>
<td>✓ 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>People with two or more atypical nevi should be referred to a dermatologist for education about self-monitoring.</td>
<td>✓ 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>National Institute for Health and Clinical Excellence (2006)</td>
<td>Patients from high risk groups at high risk of skin cancer should be counseled about sun protection.</td>
<td>✓ 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients with two or more atypical naevi, giant congenital naevi (where there is suspicion of transformation) should be referred to a skin cancer health service team for education.</td>
<td>✓ 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients at high risk of recurrence or new primary cancers should be instructed in self-examination</td>
<td>✓ 10,11</td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>Institution</td>
<td>Recommendation</td>
<td>Outcome of interest</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>--------------------</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>Royal College of Surgeons(^{12}) (2009)</td>
<td>Individuals identified as higher risk should be advised about appropriate methods for sun avoidance and protection.</td>
<td>✓ 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Individuals identified as higher risk should be educated and encouraged to perform self-examination of the skin.</td>
<td>✓ 3,10</td>
<td></td>
</tr>
<tr>
<td>Scottish</td>
<td>Scottish Intercollegiate Guidelines Network(^{22}) (2003)</td>
<td>Individuals at higher risk should be educated about awareness of risk factors and appropriate methods of sun protection.</td>
<td>✓ 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Individuals at higher risk should be educated about the diagnostic features of melanoma.</td>
<td>✓ 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Individuals at higher risk should be encouraged to perform self-examination of the skin.</td>
<td>✓ 10</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>SCHIN(^{23}) (2011)</td>
<td>If patients are at higher risk for melanoma they should be referred for education on self-examination and provided with written and photographic information.</td>
<td>✓ 3,5,10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Importance of avoiding sun beds and sunlamps is heightened in high risk groups.</td>
<td>✓ 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>For all patients at increased risk of melanoma monthly self-examinations should be encouraged.</td>
<td>✓ 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>For all patients at increased risk of melanoma advise on prevention of skin cancer</td>
<td>✓ 9</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>American Academy of Dermatology(^{42}) (2011)</td>
<td>Educate patients in monthly self-examinations of their skin.</td>
<td>✓ 3,10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>American Society of Plastic Surgeons(^{33}) (2009)</td>
<td>Individuals with high risk features should be instructed on how to perform regular self-examinations</td>
<td>✓ 3,10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>National Comprehensive Cancer Network(^{34}) (2013)</td>
<td>All patients and their families should receive skin cancer prevention education, including sun protection measures.</td>
<td>✓ 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Educate patients in monthly self skin exam and lymph node self exam.(^{a})</td>
<td>✓ 3,10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tanning beds should be avoided.(^{a})</td>
<td>✓ 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>High risk individuals should be advised regarding sun protection and signs of melanoma.</td>
<td>✓ 3,9,10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>National Cancer Institute(^{35}) (2012)</td>
<td>Patients should be educated about avoiding intermittent exposure to UV radiation, both solar and non-solar.(^{a})</td>
<td>✓ 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tanning beds should be avoided.(^{a})</td>
<td>✓ 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>High risk patients, including first-degree family members in melanoma–prone families should be educated about sun safety and warning signs of melanoma.</td>
<td>✓ 9,10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>High risk patients should understand the application of sunscreen should not be used to prolong time in the sun.</td>
<td>✓ 9</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) Recommendation for all patients
\(^{b}\) Abbreviations ACNMGRWP: Australian Cancer Network Melanoma Guidelines Revision Working Party; EDF, EADO, EORTC: European Dermatology Forum, European Association of Dermato-Oncology and European Organisation for Research and Treatment of Cancer; SCHIN: Sowerby Centre for Health Informatics at Newcastle

Outcome of interest:
1. Identification of high risk groups.
2. Increased monitoring.
3. Early detection of melanoma.
4. Improved prognosis.
5. Decreased morbidity.
6. Reduction in unnecessary excisions.
7. Improved diagnostic accuracy.
8. Improved sensitivity and sensitivity.
10. Improve patient’s ability to detect changes on the skin.
11. Improve patient support (psychological outcomes).

*Outcome not provided
4 Characteristics of individuals at higher risk of developing melanoma

4.1 Preamble

This chapter provides the first of two papers submitted for publication using data from the Melanoma Patterns of Care study. This chapter examines the characteristics of individuals at higher risk of developing melanoma and the clinical features associated with their melanomas.

Authors

C.G. Watts¹, C. Madronio¹, R.L. Morton², C. Goumas³, B.K. Armstrong¹, A. Curtin⁴, S.W. Menzies⁵, G.J. Mann³,⁶, J.F. Thompson³, A.E. Cust¹,³

Affiliations

¹ Cancer Epidemiology and Prevention Research, Sydney School of Public Health, The University of Sydney, Sydney, NSW, Australia
² NHMRC Clinical Trials Centre, The University of Sydney, Sydney, NSW Australia
³ Melanoma Institute Australia, The University of Sydney, North Sydney, NSW, Australia
⁴ School of Public Health, Rural Health Northern Rivers, Lismore, NSW, Australia
⁵ Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital, and the Discipline of Dermatology, The University of Sydney, Sydney, NSW, Australia
⁶ Centre for Cancer Research, Westmead Institute for Medical Research, The University of Sydney, Westmead, NSW, Australia
4.2 Abstract

We aimed to characterise melanoma patients and the clinical features associated with their melanomas according to patient risk factors, to assist with improving the identification and management of a higher-risk subgroup. The Melanoma Patterns of Care study was a population-based, observational study based on doctors’ reported clinical management of melanoma patients in New South Wales, Australia, diagnosed with an in situ or invasive primary melanoma over a 12-month period. Of 2,727 patients with melanoma, 1,052 (39%) were defined as higher risk due to a family history of melanoma, multiple primary melanomas, or many naevi. Compared to melanoma patients at lower risk (i.e. without any of these risk factors), the higher risk group had a younger mean age at diagnosis (62 vs 65 years, \(p<0.001\)), but this differed by risk factor (56 years for patients with a family history, 59 years for those with many naevi and 69 years for those with a previous melanoma). These age differences were consistent across all body sites. Among higher risk patients, those with many naevi were more likely to have melanoma on the trunk (41% vs 29%, \(p<0.001\)), those with a family history of melanoma were more likely to have melanomas on the limbs (57% vs 42%, \(p<0.001\)), and those with a personal history were more likely to have melanoma on the head and neck (21% vs 15%, \(p=0.003\)). Our findings suggest that a person’s risk factor status could be used to tailor surveillance programs and education about skin self-examination.

4.3 Introduction

Cutaneous melanoma incidence is increasing in predominantly European populations.\(^1\)

Australia’s incidence is amongst the highest in the world,\(^2\) and for young Australian adults aged 15–44 years, melanoma is the most common malignancy and one of the leading causes of cancer death.\(^3\)
Australian\textsuperscript{4} and international\textsuperscript{5} clinical practice guidelines for management of cutaneous melanoma recommend that people at higher risk of melanoma consider having regular surveillance and be educated about skin self-examination and appropriate sun protection. Number of naevi, family history of melanoma and a history of multiple primary melanomas are among the strongest risk factors for developing a first or subsequent melanoma.\textsuperscript{6-8} Further characterisation of individuals with these risk factors, and of the clinical features associated with their melanomas, may assist in the identification and clinical management of this higher risk subgroup and could improve our understanding of the aetiological heterogeneity of melanoma.

The Melanoma Patterns of Care study documented the characteristics and clinical management of people diagnosed with melanoma in New South Wales (NSW), Australia, over a 12-month period. We aimed to describe patient and melanoma characteristics, including age at diagnosis, histopathological tumour characteristics and body site of the melanoma, for those identified as having either many naevi, or a family or personal history of melanoma (i.e. higher risk patients), and to compare these characteristics to those of lower risk patients without these risk factors.

\subsection{4.4 Materials and Methods}

\subsubsection{4.4.1 Study sample}

The Melanoma Patterns of Care study was a population-based, observational study based on doctors’ reported management of melanoma patients residing in NSW, Australia, with a new histopathologically confirmed primary in situ or invasive cutaneous or unknown primary site
melanoma (ICD-O-3 site codes C44.0 to C44.9 and C80.9; morphology codes 8720-8790 /2 or /3)⁹ reported to the NSW Central Cancer Registry in the 12 months from 23 October 2006. NSW is the most populous state in Australia and includes about a third of the Australian population. Patients’ demographic information and degree of spread of the melanoma was obtained from the Registry. Ethics approval was granted by Human Research Ethics Committees of The University of Sydney and the Cancer Institute NSW.

4.4.2 Data collection

The ‘doctor providing initial care following diagnosis’ for this study was the referring doctor on the diagnostic pathology report on which the cancer registration was based. It is mandatory for pathologists in NSW to notify every newly diagnosed cancer to the Central Cancer Registry. For each new melanoma reported during this period, the doctor providing initial care was contacted by the study team and asked to complete a questionnaire regarding the clinical management of their patient. Doctors to whom the initial doctor referred a melanoma patient were also contacted by the study team and asked to complete a questionnaire. Supplementary Figure S4.1 describes this process. Whilst all invasive melanomas were captured and followed during the study period, questionnaire responses were only sought for the first 450 notifications of in situ melanomas, to minimise workload. Trained field-workers assisted with completion of questionnaires using patient records, when requested by doctors with large numbers of patients.

Questionnaires were completed for 2,758 of 3,869 (71%) of patients diagnosed with melanoma during the study period. Thirty-one (1%) patients for whom risk status was not completed were excluded from this analysis. Of the remaining 2,727 patients, 1,052 (39%) were defined as higher risk of a subsequent melanoma if they had one or more of: 1) multiple
primary melanoma (i.e. a previous melanoma prior to the study period), or 2) a family history of melanoma in a blood relative, or 3) many naevi; and 1,675 (61%) patients were defined as lower risk (Supplementary Figure 4.1). Body site of the melanoma was categorised as head and neck (face, scalp ears, neck), trunk, upper limbs (including shoulders) and lower limbs (including hips). For 22 patients who were diagnosed with multiple primary melanomas during the study period, the thickest lesion was chosen for analysis. Postcode of residence was used to derive socio-economic status, based on the Index of Relative Social-Economic Disadvantage that ranks social and economic well-being, and to derive an index of remoteness based on the Rural, Remote and Metropolitan Areas classification. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was used to guide the reporting of this study.

4.4.3 Statistical analysis

Chi-square tests, t-tests, ANOVA F-tests and Wilcoxon rank sum tests were used to compare groups defined by risk factors. Linear regression was used to test for two way interactions. All analyses were conducted using SAS 9.3 (SAS Institute Inc.), with statistical significance inferred at P <0.05.

4.5 Results

4.5.1 Patient and melanoma characteristics for those at higher risk compared with those at lower risk

Table 4.1 describes the 1,052 patients classified as higher risk, the 1,675 lower-risk patients and the characteristics of their melanomas. Having many naevi (62%) was the most common
risk factor in this group, followed by personal history (42%) and family history (28%).

Higher risk patients had, on average, a higher proportion of superficial spreading melanomas than lower risk patients (49% vs 45%), fewer lentigo maligna melanomas (12% vs 15%, p=0.007), and a lower proportion of melanomas > 1mm thick (29% vs 32% p <0.001). The higher risk group had a younger mean age at diagnosis (62 years vs 65 years p <0.001), with 25% of patients younger than 50 years compared to 16% of lower-risk patients. A difference in mean age at diagnosis between higher and lower risk patients was observed for females (55.9 years vs 63.3 years, p<0.001) but not for males (65.1 vs 65.3 years, p=0.79). However, a lower mean age of diagnosis for higher risk patients compared to lower risk patients was consistent across all body sites and histological subtypes except lentigo maligna melanoma (Supplementary Table S4.1). There were similar proportions of men and women in the higher risk and lower risk groups, and they had similar socio-economic status and urban/rural locations of residence.

Higher risk patients were less likely than lower risk patients to have a melanoma situated on the head and neck (17% vs 23%) and more likely to have a melanoma diagnosed on the trunk (37% vs 34%) and limbs (46% vs 43%) (p =0.002) (Table 4.1). The relative tumour density was calculated using the method described by Pearl and Scott,\textsuperscript{13} which takes into account the proportion of skin surface area for each body site. According to their formula, a relative density of 1 indicates a uniform distribution of melanomas over the surface of the body, values above 1 indicate an excess concentration and values less than 1 indicate a lower concentration of melanomas at a particular body site. The body site with the highest concentration of melanomas relative to its skin surface area was the head and neck area region (relative tumour density 1.80 for higher risk patients and 2.58 for lower risk patients),
followed by the upper limbs (1.48 and 1.32, respectively), trunk (1.13 and 1.03, respectively), and lower limbs (0.48 and 0.45, respectively).

The pattern of melanomas on different body sites also differed by sex (Table 4.2). Within each risk group, males were more likely than females to have melanoma on the trunk and head and neck, and less likely to have melanoma on the upper and lower limbs (p <0.001).

### 4.5.2 Differences in melanoma characteristics for higher risk patients, according to risk factor

Among higher risk patients, those with many naevi were more likely to have melanoma on the trunk (41% vs 29%, p<0.001), those with family history were more likely to have melanoma on the limbs (57% vs 42%, p<0.001), and those with a personal history were more likely to have melanomas on the head and neck (21% vs 15%, p=0.003) (Table 4.3). Lentigo maligna melanoma was more common for patients with a previous primary melanoma (22%) compared to those with a family history (9%) or many naevi (10%).

Patients with a family history of melanoma or with many naevi were more likely to be diagnosed at a younger age than those with a personal history of melanoma (Table 4.3). Fifteen percent of patients with a family history of melanoma were <40 years at diagnosis compared to 9% of patients without a family history. About half (54%) of patients who had no prior melanoma history were <60 years at diagnosis. The mean age at diagnosis was 56 years for patients with a family history, 59 years for those with many naevi and 69 years for those with a previous melanoma. These differences in age at diagnosis according to risk factor were observed regardless of the body site of the melanoma (Supplementary Table S4.2). For patients with many naevi or a personal history of melanoma, the mean age at
diagnosis was lowest for melanoma on the lower limbs, followed by the upper limbs, then trunk, then the head and neck (p <0.01). Patients with a family history of melanoma also followed this pattern but the differences were not statistically significant.

### 4.6 Discussion

In this large, population-based study, those classified as being at higher risk of developing melanoma had a younger mean age at diagnosis, were less likely to have a melanoma on their head and neck region and less likely to have a lentigo maligna melanoma subtype, compared to lower risk patients. However, these characteristics differed according to the type of risk factor – presence of many naevi, family history or a personal history of melanoma.

The younger age at diagnosis for patients with a family history or many naevi is consistent with a genetic predisposition to melanoma.\(^{14-16}\) Although men and women had a different distribution of melanomas on different body sites, when compared to lower risk patients, those at higher risk consistently had a greater concentration of melanomas on the trunk and limbs, body sites that receive more intermittent sun exposure. The finding that patients with head and neck melanomas had significantly fewer naevi than patients with melanomas on the trunk has also been observed in other studies.\(^{17,18}\) These findings provide some support for the divergent pathways model of melanoma aetiology, which proposes one pathway associated with more continuously sun-exposed sites such as the face and neck; and a second pathway related to a genetic predisposition (e.g. those with a family history or many naevi) characterised by melanomas developing on intermittently exposed body sites such as the trunk and limbs and requiring less sun exposure for melanomagenesis to occur.\(^{17}\) One study found that patients with multiple primary melanomas or a family history of melanoma had fewer naevus-associated melanomas than patients with high naevus counts.\(^{19}\) For these
reasons, people with many naevi may be most likely to benefit from sequential digital dermoscopy and total body photography for ongoing surveillance.\textsuperscript{20,21} Improving patient awareness of their skin to recognise changes may also aid in early melanoma detection and improve outcomes.\textsuperscript{22} Education about skin self-examination could be tailored to a person’s risk factors, such as highlighting areas on the body where melanoma is most likely to occur, and emphasising that melanomas do not always originate from a naevus.

Lentigo maligna melanoma histological subtype is typically associated with melanomas on the head and neck, chronic sun exposure and older age,\textsuperscript{23} and in the present study this subtype was more common among lower risk patients and those with a personal history of melanoma. Lentigo maligna melanoma was the histological subtype with the highest mean age at diagnosis, and it was the only subtype that had a greater mean age at diagnosis for higher risk patients (71.9 years) than lower risk patients (70.7 years).

This population-based study had a relatively high response rate from the clinicians managing the care of melanoma patients; information was collected for 71\% of the 3,932 notifications of melanoma received at the cancer registry. A limitation was that identification of risk factors was based on doctors’ recall, and there may have been different interpretations of the risk factors. For example, the questionnaire item asked whether or not the patient had ‘many naevi’ rather than record actual neavus count, and for family history there was no ascertainment of the number of affected relatives or their relationship to the proband which would have enabled further categorisation of risk status. In addition, other melanoma risk factors, such as hair colour, skin type, previous history of keratinocytic lesions, sunburns or smoking were not collected.
In conclusion, our data indicate that individuals with many naevi or a family history of melanoma will, on average, present with melanoma at a younger age and be more likely to develop melanoma on areas normally covered by clothing (intermittently sun-exposed sites). Individuals at higher risk of developing melanoma are likely to benefit from increased surveillance including whole-body skin checks and monitoring of naevi.\textsuperscript{24,25} The results of our study suggest that a person’s risk factor status could be used to tailor their surveillance program in terms of a starting age and education about skin self-examination.

**Acknowledgements:** This study was funded by the Cancer Institute NSW (05/POC/1-06), with additional financial support given by the Melanoma Institute Australia and the NSW Melanoma Network. The authors are very grateful to these organisations for their financial and in-kind support, as well as The University of Sydney and the Royal Prince Alfred Hospital for their in-kind support, and to the doctors who took part in the study. CGW was supported by a PhD scholarship funded through a Cancer Institute NSW fellowship to AEC, and a Sydney Catalyst Top-Up Research Scholar Award. RLM was supported by a NHMRC Sidney Sax Fellowship (#1054216). AEC was supported by a NHMRC Career Development Fellowship (#1063593) and a Cancer Institute NSW Career Development Fellowship (#15/CDF/1-14).

**Conflict of interest:** None declared.
4.7 References


### 4.8 Tables and figures

**Table 4.1 Patient and melanoma characteristics for patients at higher risk of developing melanoma compared to lower risk patients**

<table>
<thead>
<tr>
<th>Higher risk characteristics$^{c}$</th>
<th>Higher risk$^{b}$</th>
<th>Lower risk</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=1,052 (%)$^{a}$</td>
<td>n=1,675 (%)$^{a}$</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td>137 (13)</td>
<td>380 (36)</td>
<td></td>
</tr>
<tr>
<td>Many naevi only</td>
<td>380 (36)</td>
<td>755 (45)</td>
<td></td>
</tr>
<tr>
<td>Personal history of melanoma only</td>
<td>231 (22)</td>
<td>210 (13)</td>
<td></td>
</tr>
<tr>
<td>Family history and personal history</td>
<td>28 (3)</td>
<td>251 (15)</td>
<td></td>
</tr>
<tr>
<td>Many naevi and personal history</td>
<td>147 (14)</td>
<td>83 (2)</td>
<td></td>
</tr>
<tr>
<td>Family history and many naevi</td>
<td>95 (9)</td>
<td>323 (20)</td>
<td></td>
</tr>
<tr>
<td>Family history, many naevi, and personal history</td>
<td>34 (3)</td>
<td>48 (3)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>Higher risk</th>
<th>Lower risk</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>111 (11)</td>
<td>121 (7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>40-49</td>
<td>146 (14)</td>
<td>155 (9)</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>197 (19)</td>
<td>313 (19)</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>211 (20)</td>
<td>394 (24)</td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>236 (22)</td>
<td>391 (23)</td>
<td></td>
</tr>
<tr>
<td>80+</td>
<td>151 (14)</td>
<td>301 (18)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>Higher risk</th>
<th>Lower risk</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>655 (62)</td>
<td>1,014 (61)</td>
<td>0.37</td>
</tr>
<tr>
<td>Female</td>
<td>397 (38)</td>
<td>661 (39)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histological subtype</th>
<th>Higher risk</th>
<th>Lower risk</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial spreading</td>
<td>519 (49)</td>
<td>755 (45)</td>
<td></td>
</tr>
<tr>
<td>Nodular</td>
<td>113 (11)</td>
<td>210 (13)</td>
<td></td>
</tr>
<tr>
<td>Lentigo maligna melanoma</td>
<td>125 (12)</td>
<td>251 (15)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>35 (3)</td>
<td>83 (2)</td>
<td></td>
</tr>
<tr>
<td>Not specified</td>
<td>260 (25)</td>
<td>376 (22)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Body site</th>
<th>Higher risk</th>
<th>Lower risk</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head &amp; neck</td>
<td>174 (17)</td>
<td>372 (23)</td>
<td></td>
</tr>
<tr>
<td>Trunk</td>
<td>381 (37)</td>
<td>550 (34)</td>
<td></td>
</tr>
<tr>
<td>Upper limbs</td>
<td>286 (27)</td>
<td>406 (25)</td>
<td></td>
</tr>
<tr>
<td>Lower limbs</td>
<td>200 (19)</td>
<td>299 (18)</td>
<td>0.002</td>
</tr>
<tr>
<td>Not specified</td>
<td>11 (1)</td>
<td>48 (1)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Breslow thickness (mm)</th>
<th>Higher risk</th>
<th>Lower risk</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-situ$^{d}$</td>
<td>99 (10)</td>
<td>211 (13)</td>
<td></td>
</tr>
<tr>
<td>0-1.00</td>
<td>638 (61)</td>
<td>912 (56)</td>
<td></td>
</tr>
<tr>
<td>1.01-2.00</td>
<td>176 (17)</td>
<td>238 (15)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>2.01-4.00</td>
<td>86 (8)</td>
<td>172 (11)</td>
<td></td>
</tr>
<tr>
<td>&gt;4.00</td>
<td>43 (4)</td>
<td>97 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Not specified</td>
<td>10</td>
<td>45</td>
<td></td>
</tr>
</tbody>
</table>

* Percentages may not add up to 100 due to rounding.

* Patients with either many naevi, and/or a family history and/or a personal history of melanoma.

* Mutually inclusive categories are shown.

* Questionnaires were completed for 310 in situ melanoma reports.
Table 4.2. Body site of melanomas according to patients’ sex and risk category

<table>
<thead>
<tr>
<th>Risk</th>
<th>Body site</th>
<th>Males</th>
<th>Females</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Higher a</td>
<td>Head &amp; neck</td>
<td>125 (19)</td>
<td>49 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Trunk</td>
<td>280 (43)</td>
<td>101 (26)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Upper limbs</td>
<td>155 (24)</td>
<td>131 (33)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lower limbs</td>
<td>87 (13)</td>
<td>113 (29)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not specified</td>
<td>8</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Lower</td>
<td>Head &amp; neck</td>
<td>239 (24)</td>
<td>133 (21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Trunk</td>
<td>409 (42)</td>
<td>141 (22)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Upper limbs</td>
<td>210 (21)</td>
<td>196 (30)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lower limbs</td>
<td>124 (13)</td>
<td>175 (27)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not specified</td>
<td>32</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

*a Patients with either many naevi, and/or a family history and/or a personal history of melanoma.
Table 4.3. Patient and melanoma characteristics for higher risk patients\textsuperscript{a} according to risk factor

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Family history n=294 (%)</th>
<th>No family history n=758 (%)</th>
<th>p-value</th>
<th>Many naevi n=656 (%)</th>
<th>Not many naevi n=396 (%)</th>
<th>p-value</th>
<th>Personal history n=440 (%)</th>
<th>No personal history n=612 (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>44 (15)</td>
<td>67 (9)</td>
<td></td>
<td></td>
<td>81 (12)</td>
<td>30 (8)</td>
<td>8 (2)</td>
<td>103 (17)</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>55 (19)</td>
<td>91 (21)</td>
<td></td>
<td></td>
<td>108 (16)</td>
<td>38 (10)</td>
<td>34 (8)</td>
<td>112 (18)</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>71 (24)</td>
<td>126 (17)</td>
<td></td>
<td></td>
<td>139 (21)</td>
<td>58 (15)</td>
<td>66 (15)</td>
<td>131 (21)</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>63 (21)</td>
<td>148 (20)</td>
<td></td>
<td></td>
<td>118 (18)</td>
<td>93 (23)</td>
<td>98 (22)</td>
<td>113 (18)</td>
<td></td>
</tr>
<tr>
<td>70+</td>
<td>61 (21)</td>
<td>326 (43)</td>
<td>&lt;0.001</td>
<td></td>
<td>210 (32)</td>
<td>177 (45)</td>
<td>&lt;0.001</td>
<td>234 (53)</td>
<td>153 (25)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>149 (51)</td>
<td>506 (67)</td>
<td>&lt;0.001</td>
<td></td>
<td>416 (63)</td>
<td>239 (60)</td>
<td>0.32</td>
<td>307 (70)</td>
<td>348 (57)</td>
</tr>
<tr>
<td>Female</td>
<td>145 (49)</td>
<td>252 (23)</td>
<td>&lt;0.001</td>
<td></td>
<td>240 (37)</td>
<td>157 (40)</td>
<td>0.32</td>
<td>133 (30)</td>
<td>264 (43)</td>
</tr>
<tr>
<td><strong>Histological subtype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial spreading</td>
<td>174 (59)</td>
<td>345 (46)</td>
<td></td>
<td></td>
<td>322 (49)</td>
<td>197 (50)</td>
<td>197 (59)</td>
<td>322 (53)</td>
<td></td>
</tr>
<tr>
<td>Nodular</td>
<td>34 (12)</td>
<td>79 (10)</td>
<td></td>
<td></td>
<td>78 (12)</td>
<td>35 (9)</td>
<td>44 (13)</td>
<td>69 (11)</td>
<td></td>
</tr>
<tr>
<td>Lentigo maligna melanoma</td>
<td>25 (9)</td>
<td>100 (13)</td>
<td></td>
<td></td>
<td>65 (10)</td>
<td>60 (15)</td>
<td>72 (22)</td>
<td>53 (9)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (2)</td>
<td>30 (4)</td>
<td></td>
<td></td>
<td>22 (3)</td>
<td>13 (3)</td>
<td>21 (6)</td>
<td>14 (2)</td>
<td></td>
</tr>
<tr>
<td>Not specified</td>
<td>56 (19)</td>
<td>204 (27)</td>
<td>&lt;0.001</td>
<td></td>
<td>169 (26)</td>
<td>91 (23)</td>
<td>0.07</td>
<td>106 (24)</td>
<td>154 (25)</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head &amp; neck</td>
<td>41 (14)</td>
<td>133 (18)</td>
<td>&lt;0.001</td>
<td></td>
<td>89 (14)</td>
<td>85 (22)</td>
<td>94 (21)</td>
<td>39 (15)</td>
<td></td>
</tr>
<tr>
<td>Trunk</td>
<td>83 (28)</td>
<td>298 (40)</td>
<td></td>
<td></td>
<td>269 (41)</td>
<td>112 (29)</td>
<td>144 (33)</td>
<td>81 (39)</td>
<td></td>
</tr>
<tr>
<td>Upper limbs</td>
<td>98 (33)</td>
<td>188 (25)</td>
<td></td>
<td></td>
<td>172 (27)</td>
<td>114 (29)</td>
<td>114 (26)</td>
<td>98 (28)</td>
<td></td>
</tr>
<tr>
<td>Lower limbs</td>
<td>72 (24)</td>
<td>128 (17)</td>
<td>&lt;0.001</td>
<td></td>
<td>119 (18)</td>
<td>81 (21)</td>
<td>&lt;0.001</td>
<td>83 (19)</td>
<td>70 (19)</td>
</tr>
<tr>
<td>Not specified</td>
<td>0</td>
<td>11</td>
<td></td>
<td></td>
<td>7</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td><strong>Breslow thickness (mm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-situ\textsuperscript{2}</td>
<td>24 (8)</td>
<td>75 (10)</td>
<td></td>
<td></td>
<td>64 (10)</td>
<td>35 (9)</td>
<td>48 (11)</td>
<td>51 (8)</td>
<td></td>
</tr>
<tr>
<td>0-1.00</td>
<td>175 (60)</td>
<td>463 (62)</td>
<td></td>
<td></td>
<td>392 (60)</td>
<td>246 (63)</td>
<td>264 (61)</td>
<td>374 (62)</td>
<td></td>
</tr>
<tr>
<td>1.01-2.00</td>
<td>64 (22)</td>
<td>112 (15)</td>
<td></td>
<td></td>
<td>121 (19)</td>
<td>55 (14)</td>
<td>60 (13)</td>
<td>116 (19)</td>
<td></td>
</tr>
<tr>
<td>2.01-4.00</td>
<td>20 (7)</td>
<td>66 (9)</td>
<td></td>
<td></td>
<td>49 (8)</td>
<td>37 (9)</td>
<td>45 (10)</td>
<td>41 (7)</td>
<td></td>
</tr>
<tr>
<td>&gt;4.00</td>
<td>9 (3)</td>
<td>34 (5)</td>
<td>0.06</td>
<td></td>
<td>26 (4)</td>
<td>17 (14)</td>
<td>0.33</td>
<td>19 (4)</td>
<td>24 (4)</td>
</tr>
<tr>
<td>Not specified</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Groups are not mutually exclusive, i.e. patients with more than one risk factor are included in each relevant group.
* Questionnaires were completed for 310 in situ melanoma reports.
### 4.9 Supplementary materials

#### Supplementary Table S4.1. Age at diagnosis according to patients’ melanoma characteristics and risk category

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n=1,052</th>
<th>Higher risk Mean age (SD)</th>
<th>p-value</th>
<th>n=1,675</th>
<th>Lower risk Mean age (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>655</td>
<td>65.1 (15.1)</td>
<td></td>
<td>1,014</td>
<td>65.3 (14.8)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>397</td>
<td>55.9 (16.5)</td>
<td>p&lt;0.001</td>
<td>661</td>
<td>63.3 (16.2)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Histological subtype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial spreading</td>
<td>519</td>
<td>58.8 (16.1)</td>
<td></td>
<td>755</td>
<td>61.8 (15.5)</td>
<td></td>
</tr>
<tr>
<td>Nodular</td>
<td>113</td>
<td>62.6 (16.0)</td>
<td></td>
<td>210</td>
<td>68.2 (16.4)</td>
<td></td>
</tr>
<tr>
<td>Lentigo maligna melanoma</td>
<td>125</td>
<td>71.9 (11.0)</td>
<td></td>
<td>251</td>
<td>70.7 (11.4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>35</td>
<td>62.1 (16.4)</td>
<td>p&lt;0.001</td>
<td>83</td>
<td>67.6 (15.9)</td>
<td></td>
</tr>
<tr>
<td>Not specified</td>
<td>260</td>
<td>61.6 (16.6)</td>
<td>p&lt;0.001</td>
<td>376</td>
<td>62.9 (15.4)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>Body site</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>174</td>
<td>66.3 (16.3)</td>
<td></td>
<td>372</td>
<td>68.4 (15.6)</td>
<td></td>
</tr>
<tr>
<td>Trunk</td>
<td>381</td>
<td>61.7 (16.0)</td>
<td></td>
<td>550</td>
<td>63.7 (14.6)</td>
<td></td>
</tr>
<tr>
<td>Upper limbs</td>
<td>286</td>
<td>60.2 (15.7)</td>
<td></td>
<td>406</td>
<td>63.6 (15.2)</td>
<td></td>
</tr>
<tr>
<td>Lower limbs</td>
<td>200</td>
<td>59.0 (16.0)</td>
<td>p&lt;0.001</td>
<td>299</td>
<td>62.2 (15.8)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Not specified</td>
<td>5</td>
<td></td>
<td></td>
<td>13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Supplementary Table S4.2. Mean age at diagnosis for higher risk patients\(^a\) according to body site of melanoma and risk factor

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Family history</th>
<th>No family history</th>
<th>Many naevi</th>
<th>Not many naevi</th>
<th>Personal history</th>
<th>No personal history</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=294</td>
<td>n=758</td>
<td>n=656</td>
<td>n=396</td>
<td>n=440</td>
<td>n=612</td>
</tr>
<tr>
<td></td>
<td>mean age (SD)</td>
<td>mean age (SD)</td>
<td>mean age (SD)</td>
<td>mean age (SD)</td>
<td>mean age (SD)</td>
<td>mean age (SD)</td>
</tr>
<tr>
<td>Mean age at diagnosis p-value(^b)</td>
<td>56.0 (15.1)</td>
<td>63.7 (16.1)</td>
<td>59.4 (16.3)</td>
<td>65.2 (15.4)</td>
<td>68.7 (13.3)</td>
<td>56.5 (16.2)</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Body site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>57.1 (17.8)</td>
<td>69.1 (14.8)</td>
<td>64.1 (15.5)</td>
<td>68.5 (16.9)</td>
<td>76.2 (11.9)</td>
<td>58.8 (17.6)</td>
</tr>
<tr>
<td>Trunk</td>
<td>56.6 (15.4)</td>
<td>63.1 (15.9)</td>
<td>60.8 (16.7)</td>
<td>63.8 (14.1)</td>
<td>67.8 (13.4)</td>
<td>58.0 (16.3)</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>55.9 (14.3)</td>
<td>62.4 (16)</td>
<td>57.3 (15.4)</td>
<td>64.6 (15.3)</td>
<td>67.2 (13.7)</td>
<td>55.6 (15.3)</td>
</tr>
<tr>
<td>Lower limbs</td>
<td>55.0 (14.7)</td>
<td>61.3 (16.3)</td>
<td>55.7 (15.7)</td>
<td>63.8 (15.2)</td>
<td>67.0 (12.8)</td>
<td>53.3 (15.7)</td>
</tr>
<tr>
<td>p-value(^c)</td>
<td>0.88</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.12</td>
<td>0.008</td>
<td>0.03</td>
</tr>
</tbody>
</table>

\(^a\) Patients with either many naevi, and/or a family history and/or a personal history of melanoma. Mutually inclusive categories are shown.

\(^b\) p-value from t-test comparing patients with and without the risk factor.

\(^c\) p-value from ANOVA F-test comparing ages by body site, within each risk category.
3,969 notifications for invasive melanoma (3,519 invasive and 450 in situ based on a subset) for 3,906 patients to NSW Central Cancer Registry 23rd October 2006 to 22nd October 2007

Eligibility criteria:
- NSW resident
- ICD-0-3 (8720-8790) ending in 2 or 3 and (C44.0-C44.9) or C80.9
- 37 reports ineligible and excluded

3,932 reports (3,869 patients) followed up
Questionnaire sent to notifying clinician

Questionnaire 1 if practice setting was
- General practice
- Skin Cancer Clinic

Questionnaire 2 if practice setting was
- Dermatology
- Surgery
- Plastic surgery
- Melanoma unit

Questionnaire 3 if metastatic disease was recorded and practice setting was
- Surgery
- Plastic surgery
- Medical oncologist
- Radiation oncologist
- Melanoma unit

A new clinician also managing patient identified on questionnaire
Questionnaire completed and returned to study team

Total patients 2,758
Total melanomas 2,782
Q1&Q2: 2,605 patients
Q1&/OR Q2&Q3: 122 patients
Q3 only: 31 patients

37 reports ineligible and excluded
31 patients excluded as risk status not completed

1,052 higher risk patients
1,675 lower risk patients

Supplementary Figure 4.1. Recruitment process for the Melanoma Patterns of Care study and identification of a higher risk group. Questionnaires were received for 2,448 patients with invasive melanoma (over a 12-month period) and 310 patients with in situ melanoma (collected over a shorter period). Patients were defined as higher risk based on questionnaire data indicating 1) a history of a previous melanoma before the study period), and/or 2) a family history of melanoma, and/or 3) many naevi.
5 Diagnosis and clinical management of individuals at higher risk of melanoma

5.1 Preamble

This chapter is the second of two papers submitted for publication using data from the Melanoma Patterns of Care study. This chapter examines the diagnosis and clinical management of melanoma patients at higher risk of a new primary melanoma.

Authors
C.G. Watts¹, C. Madronio¹, R.L. Morton², C. Goumas³, B.K. Armstrong¹, A. Curtin⁴, S.W. Menzies⁵, G.J. Mann³, G.J. Mann⁵, J.F. Thompson³, A.E. Cust¹,³

Affiliations
¹ Cancer Epidemiology and Prevention Research, Sydney School of Public Health, The University of Sydney, Sydney, NSW, Australia
² NHMRC Clinical Trials Centre, The University of Sydney, Sydney, NSW Australia
³ Melanoma Institute Australia, The University of Sydney, North Sydney, NSW, Australia
⁴ School of Public Health, Rural Health Northern Rivers, Lismore, NSW, Australia
⁵ Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital, and the Discipline of Dermatology, The University of Sydney, Sydney, NSW, Australia
⁶ Centre for Cancer Research, Westmead Institute for Medical Research, The University of Sydney, Westmead, NSW, Australia
5.2 Abstract

**Objectives:** To describe the method of diagnosis, clinical management and adherence to clinical practice guidelines for melanoma patients at higher risk of a subsequent primary melanoma, and compare this with melanoma patients at lower risk.

**Methods:** The Melanoma Patterns of Care study was a population-based, observational study based on doctors’ reported clinical management of melanoma patients in New South Wales, Australia, diagnosed with in situ or invasive melanoma over a 12-month period from October 2006. Of 2,605 patients with localised melanoma, 1,019 (39%) were defined as higher risk due to either a family history of melanoma, multiple primary melanomas, or many naevi.

**Results:** Compared to patients at lower risk, higher risk patients were more likely to receive their initial care from a primary care physician (56% vs 50%, P=0.002), have their melanoma detected during a routine skin check (40% vs 33%, P <0.001), their lesion assessed with dermoscopy (63% vs 56%, P=0.002), and be encouraged to have skin surveillance (84% vs 77%, P <0.001) and skin self-examination (87% vs 83%, P=0.03). Higher socio-economic status and urban residence were associated with higher risk patients receiving initial treatment from a specialist doctor.

**Conclusions:** Clinical management of higher risk patients was more likely to conform to clinical practice guidelines for diagnosis and skin surveillance than that of melanoma patients at lower risk.

5.3 Introduction

Melanoma is the third most common cancer in Australia for both males and females.¹ Once a person has been diagnosed with invasive or in situ melanoma, they have approximately 5 to
10-fold higher risk of subsequent melanomas compared to the general population\textsuperscript{2,3} and there are a number of environmental and genetic factors which further influence melanoma risk.\textsuperscript{4-8}

Australian\textsuperscript{9,10} and international\textsuperscript{11} clinical practice guidelines for management of cutaneous melanoma recommend that people at higher risk of new primary melanoma be considered for a surveillance program, and educated about suspicious skin changes, skin self-examination and appropriate sun protection. In addition, training in and use of dermoscopy is recommended for clinicians routinely examining suspicious lesions.\textsuperscript{9-11} Risk factors for future primary melanomas identified in the Australian guidelines\textsuperscript{9,10} include common and dysplastic naevi, family history of melanoma, history of previous melanoma or non-melanoma skin cancer, as well as age, sex, skin and hair pigmentation, and evidence of actinic skin damage.

There is limited population-level evidence describing how melanoma patients at higher risk of a new (subsequent) primary melanoma are diagnosed and managed in the population, and whether their clinical management adheres to Australian Clinical Practice Guidelines.\textsuperscript{10} To address this question, we used the Melanoma Patterns of Care study, which documented clinical care for all patients diagnosed with melanoma in New South Wales (NSW), Australia, over a 12-month period. We compared the diagnosis and clinical management of a higher risk group (having either a family history of melanoma, multiple primary melanomas, or many naevi) with that for melanoma patients at lower risk of a new primary melanoma (melanoma patients without these risk factors), and examined factors associated with higher risk patients receiving initial care from a specialist.
5.4 Materials and methods

5.4.1 Study sample

The Melanoma Patterns of Care study was a population-based, observational study based on doctors’ reported management of melanoma patients residing in NSW, Australia, who had a new histopathologically confirmed primary in situ or invasive cutaneous or unknown primary site melanoma (ICD-O-3 site codes C44.0 to C44.9 and C80.9; morphology codes 8720-8790 /0,/2 or /3)\(^\text{12}\) reported to the NSW Central Cancer Registry between 23 October 2006 and 22 October 2007. NSW is the largest state in Australia and includes about a third of the Australian population.\(^\text{13}\) Patients’ demographic information and degree of spread of the melanoma was obtained from the registry. Human Research Ethics Committees of The University of Sydney and the Cancer Institute NSW approved the project.

5.4.2 Data collection

The ‘doctor providing initial care following diagnosis’ for this study was the referring doctor on the diagnostic pathology report on which the cancer registration was based. It is mandatory for pathologists in NSW to notify every newly diagnosed cancer to the Central Cancer Registry. For each new primary melanoma reported during this period, the doctor providing initial care was contacted by the study team and asked to complete a questionnaire regarding the clinical management of their patient. Doctors to whom the initial doctor referred a melanoma patient were also contacted by the study team and asked to complete a questionnaire. Figure 5.1 describes this process. Whilst all invasive melanomas were captured and followed during the study period, questionnaire responses were sought only for the first 450 notifications of in situ melanomas, to minimise workload. Trained field workers assisted
with completion of questionnaires using documented patient records, when requested by
doctors with large numbers of patients.

One or more questionnaires were completed for 2,758 patients diagnosed with melanoma
during the study period. Patients with disease that had spread to regional or distant sites
(n=153, 6%) were excluded from this analysis in order to focus on management of localised
disease. Of those with localised disease, 1,019 (39%) were defined as being at higher risk of a
new primary melanoma, based on their questionnaires indicating either: 1) multiple primary
melanomas (i.e. a previous melanoma before the study period), and/or 2) a family history of
melanoma, and/or 3) many naevi. Melanoma patients without any of these risk factors were
defined as lower risk (n=1,586, 61%). For 22 patients who were diagnosed with multiple
primary melanomas during the study period, the melanoma with the greatest Breslow
thickness was chosen for analysis. The Strengthening the Reporting of Observational Studies
in Epidemiology (STROBE) checklist was used to guide the reporting of this study. 14

5.4.3 Statistical analysis

Chi-square and Wilcoxon rank sum tests were used to compare diagnosis and clinical
management between higher and lower risk groups, and between higher risk patients
according to type of risk factor. To examine factors associated with higher risk patients
receiving their initial care from a specialist compared to a primary care physician, prevalence
ratios and 95% confidence intervals (CI) were calculated from a log binomial regression
model 15 using the variables: age at diagnosis, sex, residence location classified from postcode
into urban or rural locations (based on the Rural, Remote and Metropolitan Areas
classification), 16 socio-economic status (measured using the Index of Relative Social-
Economic Disadvantage, 17 which ranks social and economic well-being based on area of
residence), many naevi (yes, no), histopathology of the melanoma, spread of disease at diagnosis, and patients’ travel distance between their home and initial doctor calculated using geographical information system software (ArcGIS, Release 10.1). All analyses were conducted using SAS 9.3 (SAS Institute Inc.), with statistical significance inferred at $P < 0.05$.

5.5 Results

5.5.1 Patients’ and melanomas’ characteristics for those at higher risk of subsequent primary melanoma

Of the 1,019 patients classified as being at higher risk of subsequent primary melanoma, the majority (63%) were males (Table 5.1). The median age at diagnosis was 67 years for males and 55 years for females. About half (54%) lived in the capital city, Sydney, 23% lived in other metropolitan or large rural cities, and 23% were from rural areas. The predominant type of melanoma was superficial spreading melanoma, and the median Breslow thickness of invasive melanomas was 0.6 mm (interquartile range 0.4-1.2).

5.5.2 Diagnosis and clinical management of melanoma patients at higher risk compared with those at lower risk of a new primary melanoma

Table 5.2 compares the diagnosis and management of melanoma patients at higher risk and lower risk. Melanomas of higher risk patients were more likely to be detected during a routine skin check (40% vs 33%) and less likely to be patient-reported (42% vs 48%), but higher risk and lower risk patients had a similar proportion detected incidentally by a doctor (13% vs 12%). Higher risk patients were more likely to receive their initial melanoma care from a primary care physician, either at a general practice (37%) or skin cancer clinic (19%), than were lower risk patients (35% and 16% respectively). Higher risk patients were more
likely to have their lesion assessed using dermoscopy (63% vs 56% p=0.002), to have follow-up skin surveillance recommended by a clinician (84% vs 77% P < 0.001), and to be encouraged to conduct skin self-examination (87% vs 83%, P = 0.03).

Dermatologists were more likely than primary care physicians to use dermoscopy, both for higher risk patients (88% and 66% respectively, P <0.001) and lower risk patients (83% and 58% respectively, P <0.001). Primary care physicians working in skin cancer clinics were much more likely to be using dermoscopy than primary care physicians working in general practice settings, and again this was seen for both higher risk patients (98% and 43% respectively, P <0.001) and lower risk patients (93% and 41% respectively, P <0.001).

For the higher risk group, the reason for excision was most commonly listed as ‘a change in colour’ (50%) and only 5% of lesions had been reviewed previously and reported as ‘under observation’. Melanomas detected by doctors were, on average, thinner than patient-detected melanomas (median: 0.5 mm vs 0.8 mm, P <0.001). The anatomical location also varied according to who detected the melanoma; patient-detected melanomas tended to be on the head, neck and lower limbs, whereas melanomas detected by doctors were more likely to be on the trunk and upper limbs (P <0.001).

5.5.3 Factors associated with higher risk patients receiving their initial care from a specialist rather than a primary care physician

In a multivariate regression model, greater travel distance, urban residence, and residence in a more socio-economically advantaged area were associated with initial care by a specialist (Table 5.3). The association between greater travel distance and initial specialist care was stronger for patients who lived in rural locations than urban locations (P-interaction <0.001). Tumour characteristics including histological subtype and Breslow thickness were not
significantly associated with receiving initial specialist care, and thus were not retained in the multivariate regression model.

5.5.4 Differences in clinical management of higher risk patients according to type of risk factor

Among higher risk patients, the type of risk factor influenced clinical management. Patients with many naevi were less likely than patients with a family history or multiple primary melanomas to receive initial care of their melanoma from a dermatologist (16% vs 23% respectively, P=0.006). However, patients with many naevi were more likely than patients with other risk factors to have their melanoma assessed using dermoscopy (41% vs 37%, respectively P <0.001), to be encouraged to perform skin self-examination (90% vs 84% respectively P=0.004), and to be advised on skin changes (92% vs 84% respectively P=0.002). For patients with many naevi, dermatologists were more likely than primary care physicians to be using dermoscopy (89% vs 78% respectively, P <0.001), however this depended on practice setting, as 100% of primary care physicians in skin cancer clinics reported using dermoscopy for patients with many naevi compared with 54% of primary care physicians in general practice (P <0.001).

5.6 Discussion

This population-based study of 2,605 patients with localised melanoma identified differences in diagnosis and clinical management according to the presence of additional risk factors (many naevi, family history or multiple primaries) for the development of subsequent primary melanoma. These differences included the detection of melanoma, practice setting, use of dermoscopy and skin surveillance recommendations, and in general demonstrated
better adherence to clinical practice guidelines for melanoma patients at higher risk compared to those at lower risk.

Australian and international clinical practice guidelines recommend training in the use of dermoscopy for doctors who routinely examine pigmented skin lesions, based on high levels of evidence that dermoscopy increases the diagnostic accuracy of melanoma and reduces the number of unnecessary excisions.\textsuperscript{10,18-21} A 2011 survey of Australian dermatologists reported that 98\% used dermoscopy.\textsuperscript{22} In our study, only 49\% of doctors providing the initial care to higher risk patients used dermoscopy to assess the melanoma, however when examined by clinician subgroup, the proportion was 88\% for dermatologists and 98\% for primary care physicians in skin cancer clinics (data not shown). Patients with many naevi were more likely to receive dermoscopy compared to patients with a family history of melanoma or multiple primaries, however patients with many naevi were less likely to be under the care of a dermatologist. The management of suspicious pigmented skin lesions is an important part of general practice.\textsuperscript{23,24} Improving skills in dermoscopic techniques not only assists with detection of melanomas at an early stage\textsuperscript{21,25} but also improves the specificity of the clinical diagnosis for all suspicious pigmented skin lesions;\textsuperscript{18,19} both have clear health system benefits.\textsuperscript{26}

Current Australian and international guidelines\textsuperscript{9-11} recommend that patients at high-risk of melanoma (and their partner or carer) receive education about checking and documenting suspicious lesions, to aid in the early detection of melanoma,\textsuperscript{27-29} although the scientific evidence in support of this recommendation is limited.\textsuperscript{11,27-29} Our data suggest that in NSW, these guideline recommendations for skin self-examination were largely being followed, with
over 80% of all patients receiving encouragement to do this, and the proportion was higher for those at higher risk.

Just over half of the melanomas excised from patients in the higher risk group were detected by doctors and on average were thinner than patient-detected melanomas. This finding is similar to a study in Queensland, Australia, which found that melanomas were thinner when detected by a doctor and when discovered as part of a routine skin check. Higher risk patients were more likely than lower risk patients to have their melanoma detected during a routine skin check. Barriers to performing full skin examinations in general practice include lack of skill in the use of dermoscopy and short consultation times. About one in eight melanomas was detected incidentally whilst visiting a doctor. Opportunistic screening of patients remains a challenge given appointment scheduling constraints, and emphasises the value of patient education particularly for older males in regional areas who have been found to present with later stage disease compared with males in metropolitan areas. Our study found that higher risk patients who lived in rural and socio-economically disadvantaged areas were less likely to have a specialist as their initial doctor and that travel distance was likely to affect the patient’s choice of initial doctor. However, we did not find any difference between rural and urban high risk patients in method of detection or Breslow thickness at diagnosis.

Over a third of patients enrolled in the Melanoma Patterns of Care study were identified as having high-risk characteristics. This proportion is reflective of Australia’s high melanoma incidence rates. A limitation of the questionnaire was that it did not provide sufficient detail to quantify the number of naevi or the relationships and number of family members affected by melanoma, limiting our ability to separate patients into more refined risk categories. It was
also not possible to identify if patients were already under regular surveillance prior to the diagnosis of melanoma. This study had a high response rate, with questionnaire data collected for 72% of all patients diagnosed over a 1-year period, and a 78% questionnaire completion rate. However, some questionnaires were completed by trained field workers, who depended on the information being recorded in the patients’ medical notes. The proportion of questionnaires completed by doctors rather than field-workers varied by clinician specialty; 94% of questionnaires from general practice and skin cancer clinics were doctor-completed, whereas 53% of specialist questionnaires were doctor-completed. In addition, we included questionnaires from initial and referral doctors in our study and were able to assess plans for follow-up, but because the study was not longitudinal we could not document what follow-up actually occurred over a longer period of time. Finally, in this study, we defined higher risk patients as those with a personal or family history of melanoma, or with many naevi, which are factors that could indicate a genetic susceptibility to melanoma.36 However, there are other risk factors for melanoma which we did not measure, such as excessive sun exposure, sunburn, non-melanoma skin cancer, pigmentedary characteristics,6 indoor tanning,37,38 immunosuppression,39 and history of childhood cancer and radiation treatment.40

This population-based study on the diagnosis and management of patients at higher risk of a new primary melanoma, suggests that management of higher risk melanoma patients was more likely to conform to clinical practice guidelines for diagnosis and ongoing skin surveillance when compared to melanoma patients at lower risk. These data will be helpful for guiding strategies for further improving population-level melanoma care and outcomes.
**Acknowledgements:** The authors are very grateful to The University of Sydney and the Royal Prince Alfred Hospital for their in-kind support, and to the doctors who took part in the study.
5.7 References


### 5.8 Tables and Figures

**Table 5.1. Patient and melanoma characteristics for patients at high-risk of developing a new primary melanoma**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Higher risk&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Lower risk&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=1,019 N (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>N=1,586 N (%)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Age at diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>103 (10)</td>
<td>108 (7)</td>
</tr>
<tr>
<td>40-49</td>
<td>141 (14)</td>
<td>142 (9)</td>
</tr>
<tr>
<td>50-59</td>
<td>191 (19)</td>
<td>301 (19)</td>
</tr>
<tr>
<td>60-69</td>
<td>206 (20)</td>
<td>370 (23)</td>
</tr>
<tr>
<td>70-79</td>
<td>232 (23)</td>
<td>377 (24)</td>
</tr>
<tr>
<td>80+</td>
<td>146 (14)</td>
<td>288 (18)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>637 (63)</td>
<td>959 (60)</td>
</tr>
<tr>
<td>Female</td>
<td>382 (37)</td>
<td>627 (40)</td>
</tr>
<tr>
<td><strong>Histological subtype</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial spreading</td>
<td>508 (50)</td>
<td>738 (47)</td>
</tr>
<tr>
<td>Nodular</td>
<td>104 (10)</td>
<td>188 (12)</td>
</tr>
<tr>
<td>Lentigo maligna melanoma</td>
<td>123 (12)</td>
<td>250 (16)</td>
</tr>
<tr>
<td>Other</td>
<td>33 (3)</td>
<td>73 (5)</td>
</tr>
<tr>
<td>Not defined</td>
<td>251 (25)</td>
<td>337 (21)</td>
</tr>
<tr>
<td><strong>Breslow thickness (mm)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-situ&lt;sup&gt;c&lt;/sup&gt;</td>
<td>99 (10)</td>
<td>211 (13)</td>
</tr>
<tr>
<td>0-1.00</td>
<td>634 (62)</td>
<td>904 (57)</td>
</tr>
<tr>
<td>1.01-2.00</td>
<td>166 (16)</td>
<td>221 (12)</td>
</tr>
<tr>
<td>2.01-4.00</td>
<td>78 (8)</td>
<td>154 (10)</td>
</tr>
<tr>
<td>&gt;4.00</td>
<td>37 (4)</td>
<td>87 (6)</td>
</tr>
<tr>
<td>Not otherwise specified</td>
<td>5 (0)</td>
<td>9 (0)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Higher-risk patients were identified as having one or more high-risk features: many naevi, family history or personal history of melanoma.

<sup>b</sup>Percentages may not sum to 100 due to rounding.

<sup>c</sup>In situ melanoma reports were collected during a limited period.
Table 5.2. Diagnosis and clinical management of melanoma patients at high-risk compared to those at lower risk of developing a new primary melanoma

<table>
<thead>
<tr>
<th>Diagnosis and management factors</th>
<th>Higher-risk&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Lower risk</th>
<th>P-value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=1,019</td>
<td>N=1,586</td>
<td></td>
</tr>
<tr>
<td>Specialty of initial clinician</td>
<td>N (%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>N (%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>General Practice</td>
<td>566 (56)</td>
<td>806 (51)</td>
<td></td>
</tr>
<tr>
<td>Dermatology</td>
<td>264 (26)</td>
<td>418 (26)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>116 (11)</td>
<td>231 (15)</td>
<td></td>
</tr>
<tr>
<td>Plastic surgery/other</td>
<td>67 (7)</td>
<td>129 (8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Unrecorded</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Practice setting of initial clinician</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Practice</td>
<td>378 (37)</td>
<td>552 (35)</td>
<td></td>
</tr>
<tr>
<td>Skin Cancer Clinic</td>
<td>188 (19)</td>
<td>254 (16)</td>
<td></td>
</tr>
<tr>
<td>Dermatology</td>
<td>264 (26)</td>
<td>418 (26)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>116 (11)</td>
<td>231 (15)</td>
<td></td>
</tr>
<tr>
<td>Plastic surgery</td>
<td>51 (5)</td>
<td>124 (8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Melanoma Unit</td>
<td>16 (2)</td>
<td>5 (0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Unrecorded</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Detection of melanoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient reported</td>
<td>399 (42)</td>
<td>696 (48)</td>
<td></td>
</tr>
<tr>
<td>Found incidentally by doctor</td>
<td>121 (13)</td>
<td>173 (12)</td>
<td></td>
</tr>
<tr>
<td>Routine skin check</td>
<td>385 (40)</td>
<td>469 (33)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>46 (5)</td>
<td>102 (7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Don’t know</td>
<td>55</td>
<td>121</td>
<td></td>
</tr>
<tr>
<td>Unrecorded</td>
<td>13</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Assess lesion with dermoscopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>540 (63)</td>
<td>758 (56)</td>
<td>0.002</td>
</tr>
<tr>
<td>No</td>
<td>321 (37)</td>
<td>596 (44)</td>
<td></td>
</tr>
<tr>
<td>Don’t know</td>
<td>132</td>
<td>190</td>
<td></td>
</tr>
<tr>
<td>Unrecorded</td>
<td>26</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Practice setting of follow-up clinician</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Practice</td>
<td>145 (16)</td>
<td>265 (19)</td>
<td></td>
</tr>
<tr>
<td>Skin cancer clinic</td>
<td>137 (15)</td>
<td>194 (14)</td>
<td></td>
</tr>
<tr>
<td>Dermatology</td>
<td>233 (25)</td>
<td>362 (26)</td>
<td></td>
</tr>
<tr>
<td>Surgeon</td>
<td>337 (37)</td>
<td>517 (37)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>73 (0)</td>
<td>75 (5)</td>
<td>0.08</td>
</tr>
<tr>
<td>Unrecorded</td>
<td>94</td>
<td>173</td>
<td></td>
</tr>
</tbody>
</table>

Advise patient on changes
Higher-risk patients were identified as having one or more high-risk features: many naevi, family or personal history of melanoma.

Don't know and unrecorded values were excluded from the P-value estimations.

Percentages may not sum to 100 due to rounding.

<table>
<thead>
<tr>
<th></th>
<th>Count</th>
<th>Percentage</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>775 (88)</td>
<td>1,166 (88)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>101 (12)</td>
<td>161 (12)</td>
<td>0.67</td>
</tr>
<tr>
<td>Unrecorded</td>
<td>143</td>
<td>259</td>
<td></td>
</tr>
</tbody>
</table>

Encourage skin self-exam

<table>
<thead>
<tr>
<th></th>
<th>Count</th>
<th>Percentage</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>731 (87)</td>
<td>1,065 (83)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>113 (13)</td>
<td>216 (17)</td>
<td>0.03</td>
</tr>
<tr>
<td>Unrecorded</td>
<td>175</td>
<td>305</td>
<td></td>
</tr>
</tbody>
</table>

Recommend skin surveillance

<table>
<thead>
<tr>
<th></th>
<th>Count</th>
<th>Percentage</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>680 (84)</td>
<td>951 (77)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>129 (16)</td>
<td>284 (23)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Unrecorded</td>
<td>210</td>
<td>351</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Higher-risk patients were identified as having one or more high-risk features: many naevi, family or personal history of melanoma.

\(^b\) Don't know and unrecorded values were excluded from the P-value estimations.

\(^c\) Percentages may not sum to 100 due to rounding.
Table 5.3. Multivariate prevalence ratios for higher risk patients consulting a specialist rather than a general practitioner as the initial doctor following melanoma diagnosis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>General Practice/ Skin clinic N=563\textsuperscript{a} N (%)</th>
<th>Specialist N=441\textsuperscript{a} N (%)</th>
<th>Prevalence ratio\textsuperscript{a} (95% confidence interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>61</td>
<td>42</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>90</td>
<td>50</td>
<td>0.99 (0.91-1.07)</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>111</td>
<td>79</td>
<td>1.01 (0.93-1.09)</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>106</td>
<td>96</td>
<td>1.03 (0.95-1.11)</td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>120</td>
<td>108</td>
<td>1.03 (0.95-1.11)</td>
<td></td>
</tr>
<tr>
<td>80+</td>
<td>75</td>
<td>66</td>
<td>1.05 (0.96-1.14)</td>
<td>0.76</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>360</td>
<td>266</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>203</td>
<td>175</td>
<td>1.03 (0.99-1.07)</td>
<td>0.19</td>
</tr>
<tr>
<td>Patient location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>355</td>
<td>357</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>208</td>
<td>84</td>
<td>0.93 (0.88-0.98)</td>
<td>0.009</td>
</tr>
<tr>
<td>Socio economic status\textsuperscript{b}</td>
<td>1\textsuperscript{st} Quintile (least advantaged)</td>
<td>2\textsuperscript{nd} Quintile</td>
<td>3\textsuperscript{rd} Quintile</td>
<td>4\textsuperscript{th} Quintile</td>
</tr>
<tr>
<td>1\textsuperscript{st} Quintile (least advantaged)</td>
<td>67</td>
<td>42</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>2\textsuperscript{nd} Quintile</td>
<td>137</td>
<td>49</td>
<td>0.94 (0.87-1.03)</td>
<td></td>
</tr>
<tr>
<td>3\textsuperscript{rd} Quintile</td>
<td>157</td>
<td>95</td>
<td>1.00 (0.93-1.07)</td>
<td></td>
</tr>
<tr>
<td>4\textsuperscript{th} Quintile</td>
<td>93</td>
<td>75</td>
<td>1.02 (0.94-1.10)</td>
<td></td>
</tr>
<tr>
<td>5\textsuperscript{th} Quintile (most advantaged)</td>
<td>109</td>
<td>180</td>
<td>1.07 (0.99-1.15)</td>
<td>0.01</td>
</tr>
<tr>
<td>Many naevi</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>187</td>
<td>187</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>376</td>
<td>254</td>
<td>0.97 (0.93-1.01)</td>
<td>0.18</td>
</tr>
<tr>
<td>Travel distance (km) to initial doctor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>291</td>
<td>176</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>10-19</td>
<td>67</td>
<td>82</td>
<td>1.05 (0.99-1.11)</td>
<td></td>
</tr>
<tr>
<td>20-49</td>
<td>59</td>
<td>62</td>
<td>1.06 (0.99-1.13)</td>
<td></td>
</tr>
<tr>
<td>50+</td>
<td>23</td>
<td>76</td>
<td>1.17 (1.10-1.24)</td>
<td></td>
</tr>
<tr>
<td>Unrecorded</td>
<td>123</td>
<td>45</td>
<td>0.97 (0.91-1.03)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Analysis excluded 15 higher-risk patients who were missing one or more values for these variables.

\textsuperscript{b} Prevalence ratio calculated from log binomial regression model
Index for Relative Socioeconomic Disadvantage quintiles, based on postcode of residence. People in the 1st quintile live in areas of most social disadvantage and in the 5th quintile in areas of least social disadvantage.
3,520 notifications for invasive melanoma (+450 insitu) to NSW Central Cancer Registry 23rd October 2006 to 22nd October 2007

Notifying clinician identified if:
NSW resident
ICD-10-03 (8720-8790) ending in 0,2 or 3
ICD-10-AM (C44.0-C44.) or C80.9

Questionnaire sent to notifying clinician
Questionnaire 1 if practice setting was
General practice
Skin Cancer Clinic
Questionnaire 2 if practice setting was
Dermatology
Surgery
Plastic surgery
Melanoma unit
Questionnaire 3 if metastatic disease was recorded and practice setting was
Surgery
Plastic surgery
Medical oncologist
Radiation oncologist
Melanoma unit

A new clinician identified on questionnaire
Questionnaire completed and returned to study team

Questionnaires sent to referral clinician
Questionnaire 1 completed
2,021 sent
1,473 completed
for 1,436 patients

Questionnaire 2 completed
2,929 sent
2,378 completed
for 1,955 patients

Questionnaire 3 completed
264 sent
206 completed
for 131 patients

Total patients 2,758

153 patients with Stage III or IV disease
310 patients with insitu melanoma
2,295 patients with localised invasive disease

1,019 high-risk patients
1,586 average-risk patients

Figure 5.1 Flow chart describing data collection in the Melanoma Patterns of Care study, and the categorisation of higher risk and lower risk groups. Follow-up for in situ melanomas was ceased after 450 notifications were received. Patients were defined as high-risk based on questionnaire data indicating either 1) a history of a previous melanoma before the study period, and/or 2) a family history of melanoma, and/or 3) many naevi.
6 Specialised surveillance for individuals at high risk of melanoma: a cost analysis of a ‘High Risk Clinic’.

6.1 Preamble

This chapter describes the surveillance and treatment undertaken at the High Risk Clinic and the results of the micro-costing study from which we calculated of a mean cost per patient for surveillance, from both a health system and societal perspective.
Specialized Surveillance for Individuals at High Risk for Melanoma
A Cost Analysis of a High-Risk Clinic

Caroline G. Watts, MPH; Anne E. Cust, MPH (Hons), PhD; Scott W. Menzies, MBBS, PhD; Elliot Coates, BSc (Hons), MBBS; Graham J. Mann, MBBS, PhD; Rachael L. Morton, MScMed (ClinEpi) (Hons), PhD

IMPORTANCE Regular surveillance of individuals at high risk for cutaneous melanoma improves early detection and reduces unnecessary excisions; however, a cost analysis of this specialized service has not been undertaken.

OBJECTIVE To determine the mean cost per patient of surveillance in a high-risk clinic from the health service and societal perspectives.

DESIGN, SETTING, AND PARTICIPANTS We used a bottom-up microcosting method to measure resource use in a consecutive sample of 102 patients treated in a high-risk hospital-based clinic in Australia during a 12-month period.

EXPOSURE Surveillance and treatment of melanoma.

MAIN OUTCOMES AND MEASURES All surveillance and treatment procedures were identified through direct observation, review of medical records, and interviews with staff and were valued using scheduled fees from the Australian government. Societal costs included transportation and loss of productivity.

RESULTS The mean number of clinic visits per year was 2.7 (95% CI, 2.5-2.8) for surveillance and 3.8 (95% CI, 3.4-4.1) for patients requiring surgical excisions. The mean annual cost per patient to the health system was A $882 (95% CI, A $783-$982) (US $599 [95% CI, US $532-$665]); the cost discounted across 20 years was A $11 546 (95% CI, A $10 263-$12 829) (US $7839 [95% CI, US $6969-$8710]). The mean annual societal cost per patient (excluding health system costs) was A $972 (95% CI, A $899-$1045) (US $660 [95% CI, US $611-$710]); the cost discounted across 20 years was A $12 721 (95% CI, A $12 554-$14 463) (US $8637 [95% CI, US $8523-$9820]). Diagnosis of melanoma or nonmelanoma skin cancer and frequent excisions for benign lesions in a relatively small number of patients was responsible for positively skewed health system costs.

CONCLUSIONS AND RELEVANCE Microcosting techniques provide an accurate cost estimate for the provision of a specialized service. The high societal cost reflects the time that patients are willing to invest to attend the high-risk clinic. This alternative model of care for a high-risk population has relevance for decision making about health policy.
Australia has the highest incidence of melanoma in the world. Despite this statistic and the known risk factors for melanoma, screening in the general population is not recommended at present. Selected studies have shown that screening among men older than 50 years as a one-time intervention or at 5-year intervals using primary care physicians may be cost-effective. The regular surveillance of individuals at high risk for melanoma in a specialized clinic has demonstrated improvements in early detection of lesions and a reduction in unnecessary excisions; however, to our knowledge no studies have examined whether monitoring people at very high risk for developing melanoma for a long period is cost-effective. A specialized high-risk clinic (HRC) for individuals with an elevated risk for melanoma was established within a hospital outpatient clinic at the Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital, Sydney, Australia, in 2006, and this model of care is currently being evaluated and expanded in 3 more centers. Early detection underpins the rationale for surveillance of individuals at high risk for melanoma because the stage at diagnosis affects prognosis and the cost of subsequent treatment is lower when melanoma is detected at an early compared with an advanced stage.

The aim of our microcosting study was to measure (1) the cost of providing this specialized skin surveillance service to individuals at very high risk for melanoma and (2) the factors influencing variation in resource use. We aimed to calculate the direct costs of the HRC, that is, costs to the health care system, and the indirect costs not generated directly by the clinic but as a result of attending the clinic. These costs included out-of-pocket costs (eg, travel to the clinic) and the opportunity costs of time forgone in attending the clinic. Microcosting is the reference standard technique for calculating the cost of a new service when no published estimates are available. Microcosting techniques are preferred for interventions that contain a large component of labor costs and in which interpatient variation in costs is likely, making a mean cost difficult to predict. The treatment of patients at high risk for melanoma in a specialized surveillance clinic has been evaluated in only a few countries, and, to our knowledge, no studies have reviewed or evaluated the costs of the health care service or the societal costs.

Methods

Study Design
We used a cohort study design. We obtained human research ethics committee approval from the institutional review board of the Royal Prince Alfred Hospital. All participants gave oral consent for one of us (C.G.W.) to attend and observe the HRC consultations. Patients had previously given informed consent for participation in the study.

Study Sample
All patients attending the HRC met at least 1 of the following eligibility criteria: (1) dysplastic nevus syndrome and at least 1 primary invasive melanoma, (2) diagnosis of 2 or more primary invasive melanomas, (3) strong family history of melanoma (≥3 first-degree relatives with melanoma) and 1 or more personal primary invasive melanomas, or (4) presence of the CDKN2A mutation with no requirement for a history of melanoma. The strategy used for surveillance in the Sydney HRC has been described previously. In brief, this strategy involves regular extended-length consultations once every 6 months, which include a full-body skin examination augmented with dermoscopy and the use of total body photography plus dermoscopy when indicated. When a suspected lesion is identified, the lesion is excised or sequential digital dermoscopic imaging of the lesion is commenced and the patient returns for nevus monitoring in 3 months. An additional part of the program is that patients receive instruction in skin self-examination, which they are encouraged to perform using their total body photographs between appointments. A pilot study of this clinic involving 311 patients followed up for a median of 3.5 years showed effective early detection of primary melanoma and a ratio of benign to malignant lesion excision of 1.6:1 for all lesions excised.

Microcosting Approach
We used a bottom-up microcosting approach to estimate the total costs of HRC care for 12 months. All costs associated with skin surveillance and management of newly identified lesions were included. Procedures related to testing for recurrence of a previously diagnosed cutaneous melanoma, such as chest radiography, were not included because these costs did not apply to HRC surveillance costs. All identifiable direct and indirect costs were included in the analysis and adjusted to 2013 Australian dollars. A 20-year time horizon was used to estimate the lifetime costs of surveillance based on the median age of the HRC participants. We applied the Australian standard discount rate of 5% to all future costs. The methods followed published guidance on microcosting. Additional information is included in the eMethods in the Supplement.

Direct Observation
Through direct observation of the HRC from December 10, 2012, through May 14, 2013, we recorded information about each patient’s type and length of consultation (using a stopwatch) and all resource items used. Additional information regarding the mode of transport to the clinic, patient employment status, employment leave type, and requirement of a medical certificate were noted if discussed during the consultation. For employed patients, the occupational group was graded according to the Australian Bureau of Statistics classifications to determine the median wage. The presence of accompanying family members or informal caregivers was also recorded.

Staff were interviewed about their roles, the time they spent on various tasks, and their use of consumables. Information about fixed costs and capital and equipment costs was obtained from the HRC records, and prices were checked with equipment suppliers when current receipts were not available. We calculated costs for software licenses, technology maintenance and support, and overhead costs for clinic space.
A mean cost per patient for staff in the HRC was derived using salary scales from the Public Health System Awards of New South Wales Health (the state health department). Staff costs, including payroll taxes and superannuation, were estimated as an additional 20% to their base salary.

**Review of Medical Records**

Sociodemographic data were obtained from the patients’ medical records, and the return travel distance by road from the patient’s home to the clinic was calculated using residential addresses and publicly available software (Whereis; http://www.whereis.com). All documented melanoma surveillance consultations and procedures, whether conducted in the HRC or by other services (eg, primary care), were recorded from the medical records. This information included all diagnostic tests and medication use during the preceding 12 months.

**Health System Costs**

Use of health system resources was calculated for all patients, including surveillance and treatment provided as a result of attending the HRC during the previous 12 months. Resource use items were valued according to the dollar amount subsidized by the Australian government through the Medicare Benefits Schedule. The scheduled fees are set annually by the Australian government and provide a value for services against which all residents in Australia can claim a rebate of 100% for primary care services (if the service was billed in bulk) and 85% for non-primary care services. Fees for melanoma surveillance that were reimbursed by the Medicare Benefits Schedule were deducted from the hospital salary costs of the dermatology resident to avoid double counting. We allocated a primary care level B (standard-length) or C (extended-length) service, depending on the duration of the consultation. Services provided by primary care physicians in the community were counted as level B consultations. All excised lesions were sent for a pathological examination, with costs varying according to the size and site of the lesion, the number of lesions excised during a consultation, and the complexity of the biopsy material being examined. If a patient was admitted to hospital for an excision, we assigned a health system cost based on the relevant Australian refined diagnosis related groups code.

A total annual health system cost was calculated for salaries and for overhead and capital costs. A mean cost per consultation was calculated by dividing this total cost by the number of HRC consultations in 1 year (based on the mean number during the previous 6 years). This figure was used to calculate the mean annual cost per patient.

**Societal Costs**

**Patient Travel Costs**

For patients who reported their mode of travel, we calculated a mean annual travel cost. Based on the reported mode of transport, the number of trips made to the HRC, and the number of surveillance-related consultations documented in the patient’s history, we calculated a total travel cost per patient across 12 months. For air travel, a standard online ticket price was calculated. Hotel accommodation was based on the standard overnight rate for a midrange hotel located within a 5-km radius of the hospital. If individuals had consulted their local primary care physician in the community during the past 12 months for an excision or for removal of sutures related to surveillance at the HRC, a standard return travel distance of 9.6 km (6 miles) was allocated to each primary care visit.

**Out-of-Pocket Costs for Medical Treatment**

Documentation in the patient’s medical record was used to calculate the mean out-of-pocket cost for medical treatment related to HRC surveillance in the previous 12 months but not fully rebatable through the Medicare Benefits Schedule or the Pharmaceutical Benefits Scheme. All patients required an initial set of total body photographs, which were used at each visit for monitoring lesions. At the present time, patients attending the HRC do not pay for these photographs, but this cost likely will be borne by patients in the future. A set of photographs usually lasts 7 years (E.C., personal communication, May 2013); therefore, a mean cost for 7 years was calculated per patient. Mean costs borne by patients for medicines and lotions and out-of-pocket costs for specialist services were calculated based on the standard reimbursement through the Medicare Benefits Schedule or the Pharmaceutical Benefits Scheme.

**Opportunity Costs**

The value of each patient’s time to attend the HRC or to receive other related medical care during the previous 12 months was calculated using the market price of labor (ie, wages or the aged pension). Based on our observation, an HRC visit for surveillance or a related procedure required 4 hours or half a day taken from work. For patients who lived more than 100 km (62 miles) away, a full day or 8 hours was required to attend the clinic. For employed patients, we calculated the opportunity cost of time not at work based on an estimated median of full-time weekly total cash earnings by occupation group. For patients of working age whose occupation was unknown, we estimated the opportunity cost of lost personal time per visit based on a median of full-time weekly total cash earnings for all Australian employees. For patients older than 65 years who were assumed to be retired, a proportion of the weekly single pension was used. All wages were adjusted from 2012 to 2013 wage levels by 4.9%, which was the percentage change in full-time mean earnings provided by the Australian Bureau of Statistics.

**Results**

**Study Population**

All 102 consecutive patients attending the HRC on Mondays from December 10, 2012, through May 14, 2013, were included in the study (eFigure in the Supplement). Of these, 87 were continuing (prevalent) patients and 15 were new (incident) patients attending for the first time. The characteristics of the study population are summarized in Table 1.
Labor in the HRC (ie, staff salaries) was the main component of operational expenses and accounted for 50% of health system costs. Surveillance and procedures accounted for 46% of health system costs; of this group, 235 of 271 consultations (86.7%), excluding specialist consultations, were to the HRC (Table 2). The mean consultation time for a new patient was 40 minutes. All 87 prevalent patients had 2 extended-length consultations during the 12-month period, and these consultations took a mean of 31 (95% CI, 28-34) minutes. Within this group, an additional 66 consultations for nevus monitoring were performed (mean time, 11 [95% CI, 7-15] minutes). Almost half the study group (39 of 87 [45%]) commenced short-term monitoring during the 12-month period, with 1 to 6 lesions identified for short-term monitoring. Seven patients in this group had additional lesions identified for monitoring within the study period. Thirty of the 87 patients (34%) required an excision of a suspected lesion during the 12-month study period; of these, 16 (53%) had 1 lesion excised and 4 (13%) had a range of 4 to 8 excisions. The mean number of HRC visits per year was 2.7 (95% CI, 2.5-2.8) for surveillance and 3.8 (95% CI, 3.4-4.1) for patients requiring surgical excisions.

Three melanomas and 8 keratinocyte carcinomas were detected during the study period (Table 2). Patients had 12 visits to a primary care physician in the community for excision of lesions and 22 visits for removal of excision sutures. Only 1 hospital admission was documented during the study period. Costs per patient were heavily skewed to the right, with a few patients generating costs several times the mean (Figure). The higher health care costs resulted from more excisions of benign lesions with suspected melanoma features and surgical removal of melanoma and nonmelanoma skin cancers.

Mean annual societal costs were very similar to direct health care costs at A $972 (95% CI, A $899-$1045) (US $660 [95% CI, US $611-$710])30 per patient (Table 3). The greatest proportion of these costs was related to the patient’s time spent on surveillance or related activities and travel costs (Table 4). The opportunity cost of time not at work or spent attending the HRC or for a related procedure. An opportunity cost for visiting a local primary care physician for removal of sutures was not calculated because we believed the time required would not cause the same disruption to one’s daily schedule. The mean annual out-of-pocket cost for travel was A $117 (US $79) for a consultation or a procedure-related visit, and a wide variation existed in the distance patients traveled to the clinic (Table 4). The annual mean cost for travel and accommodation combined was A $407 (95% CI, A $183-$631 (US $276 [95% CI, US $124-$428])30 per person; the mean cost of traveling by car was 79% of these costs. The mean total number of consultations was less when estimating societal costs because travel time was counted only once when an excision occurred on the same day as a clinic visit. When patients had traveled long distances and an excision was determined at the HRC to be necessary, an attempt was made to organize the surgery on the same day. In our study sample this occurred 6 times.

Table 1. Characteristics of 102 Patients Included in the Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dataa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>59 (49-64)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 65 (63.7) Female 37 (36.3)</td>
</tr>
<tr>
<td>High-risk group characteristicsb</td>
<td>Dysplastic nevus syndrome and previous melanoma 66 (64.7) Multiple primary melanoma 96 (94.1) Strong family history 11 (10.8) CDKN2A mutation 4 (3.9)</td>
</tr>
<tr>
<td>Health insurance status</td>
<td>Private 70 (68.6) Public only (Medicare) 22 (21.6) Unknown 10 (9.8)</td>
</tr>
<tr>
<td>Employment statusc</td>
<td>Employed 42 (55.3) Full time 30 (71.4) Part time 8 (19.0) Unknown 4 (9.5) Not employed 4 (5.3) Retired 17 (22.4) Unknown 13 (17.1)</td>
</tr>
<tr>
<td>Occupational type for employed groupd</td>
<td>Manager/professional 14 (33.3) Technician, community, and trade workers 17 (40.5) Clerical, administrative, and sales workers 8 (19.0) Unknown 3 (7.1)</td>
</tr>
<tr>
<td>Leave type for employed group to attend clinic visitd</td>
<td>Time in lieu 19 (45.2) Annual leave/rostered day off 15 (35.7) Sick leave 4 (9.5) Unknown 4 (9.5)</td>
</tr>
<tr>
<td>Mode of transport to clinic*</td>
<td>Car 34 (44.7) Train, bus, taxi 13 (17.1) Airplane 2 (2.6) Unknown 27 (35.5)</td>
</tr>
<tr>
<td>Distance from patient’s home to clinic and return, km</td>
<td>Mean 248 Median (IQR) 56 (27-187)</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.

a Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and may not total 100.

b Patients can be in more than 1 high-risk characteristic group.

c Includes 76 patients who provided information about employment status.

d Includes 42 patients who reported employment.

* Includes 76 patients who provided information about mode of transport.

The out-of-pocket costs for medical treatment were a small component (6%) of patient costs, because only a few visits to
Table 2. Health System Costs for Patients Attending the HRC During a 12-Month Period

<table>
<thead>
<tr>
<th>Description</th>
<th>Procedure Code(a)</th>
<th>Cost per Item, A $ (c) (\text{(d)})</th>
<th>No. in 12 mo (\text{(b)})</th>
<th>Total Cost, A (\text{(c)}) (\text{(d)})</th>
<th>Cost, US $ (\text{(c)}) (\text{(d)})</th>
<th>Mean Cost per Patient per Year(b)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Consultation Type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard-length consultation ≤20 min (level B)</td>
<td>MBS 00023</td>
<td>36.30</td>
<td>95</td>
<td>3449</td>
<td>2342</td>
<td>NA</td>
</tr>
<tr>
<td>Extended-length consultation &gt;20 min (level C)</td>
<td>MBS 00036</td>
<td>70.30</td>
<td>176</td>
<td>12 373</td>
<td>8401</td>
<td>NA</td>
</tr>
<tr>
<td>Dermatologic or surgical specialist(f)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial consultation</td>
<td>MBS 00104</td>
<td>85.55</td>
<td>6</td>
<td>513</td>
<td>348</td>
<td>NA</td>
</tr>
<tr>
<td>Subsequent consultation</td>
<td>MBS 00105</td>
<td>43.00</td>
<td>10</td>
<td>430</td>
<td>292</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Total consultation</strong></td>
<td></td>
<td></td>
<td>16 765</td>
<td>11 383</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Procedures for Excisions of Skin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic biopsy of skin(g)</td>
<td>MBS 30071</td>
<td>52.20</td>
<td>7</td>
<td>314</td>
<td>213</td>
<td>NA</td>
</tr>
<tr>
<td>Diagnostic excision of skin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 mm(c)</td>
<td>MBS 31205</td>
<td>95.45</td>
<td>39</td>
<td>2930</td>
<td>2528</td>
<td>NA</td>
</tr>
<tr>
<td>10 to &lt;20 mm</td>
<td>MBS 31210</td>
<td>123.10</td>
<td>2</td>
<td>246</td>
<td>167</td>
<td>NA</td>
</tr>
<tr>
<td>Nose, ear, eyelid, or digit</td>
<td>MBS 31230</td>
<td>168.05</td>
<td>1</td>
<td>168</td>
<td>114</td>
<td>NA</td>
</tr>
<tr>
<td>Face, neck, or lower leg</td>
<td>MBS 31235</td>
<td>143.55</td>
<td>2</td>
<td>215</td>
<td>146</td>
<td>NA</td>
</tr>
<tr>
<td>Therapeutic excision on skin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nose, ear, or eyelid, &lt;10-mm SCC or BCC</td>
<td>MBS 31255</td>
<td>221.35</td>
<td>1</td>
<td>221</td>
<td>150</td>
<td>NA</td>
</tr>
<tr>
<td>Face, neck, or lower leg, &lt;10-mm SCC or BCC</td>
<td>MBS 31265</td>
<td>184.50</td>
<td>1</td>
<td>185</td>
<td>125</td>
<td>NA</td>
</tr>
<tr>
<td>Reseuction on face, neck, or lower leg, &lt;10-mm SCC or BCC</td>
<td>MBS 31266</td>
<td>184.50</td>
<td>1</td>
<td>185</td>
<td>125</td>
<td>NA</td>
</tr>
<tr>
<td>Excision of skin from other site, &lt;10-mm SCC or BCC</td>
<td>MBS 31280</td>
<td>155.85</td>
<td>4</td>
<td>623</td>
<td>423</td>
<td>NA</td>
</tr>
<tr>
<td>Reseuction of skin from other site, &lt;10-mm SCC or BCC</td>
<td>MBS 31282</td>
<td>156.40</td>
<td>1</td>
<td>156</td>
<td>106</td>
<td>NA</td>
</tr>
<tr>
<td>Excision of skin, &lt;10-mm melanoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Face, neck, or lower leg</td>
<td>MBS 31310</td>
<td>378.65</td>
<td>2</td>
<td>757</td>
<td>514</td>
<td>NA</td>
</tr>
<tr>
<td>Other site</td>
<td>MBS 31325</td>
<td>270.55</td>
<td>1</td>
<td>271</td>
<td>184</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Total skin excisions</strong></td>
<td></td>
<td></td>
<td>6271</td>
<td>4795</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequential digital dermoscopy imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 Lesions</td>
<td>MBS 30075</td>
<td>65.00</td>
<td>43</td>
<td>2795</td>
<td>1898</td>
<td>NA</td>
</tr>
<tr>
<td>&gt;3 Lesions</td>
<td>MBS 30075</td>
<td>75.00</td>
<td>3</td>
<td>225</td>
<td>153</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Total monitoring</strong></td>
<td></td>
<td></td>
<td>3020</td>
<td>2051</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Other Procedures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-stage local flap repair</td>
<td>MBS 45203</td>
<td>406.05</td>
<td>1</td>
<td>406</td>
<td>276</td>
<td>NA</td>
</tr>
<tr>
<td>Vermilionectomy</td>
<td>MBS 45669</td>
<td>326.05</td>
<td>1</td>
<td>326</td>
<td>221</td>
<td>NA</td>
</tr>
<tr>
<td>Diagnostic biopsy of lymph gland (by specialist)</td>
<td>MBS 30075</td>
<td>149.75</td>
<td>1</td>
<td>150</td>
<td>102</td>
<td>NA</td>
</tr>
<tr>
<td>Ultrasonography of the groin</td>
<td>MBS 55816</td>
<td>109.10</td>
<td>1</td>
<td>109</td>
<td>74</td>
<td>NA</td>
</tr>
<tr>
<td>Inpatient stay in standard ward (mean length of stay, 1-23 d)</td>
<td>DRG 112(f)</td>
<td>NA</td>
<td>NA</td>
<td>2043</td>
<td>1387</td>
<td>NA</td>
</tr>
<tr>
<td>Pathological examination(h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 3</td>
<td>MBS 72816</td>
<td>86.35</td>
<td>22</td>
<td>1899</td>
<td>1290</td>
<td>NA</td>
</tr>
<tr>
<td>Level 4</td>
<td>MBS 72823</td>
<td>97.13</td>
<td>39</td>
<td>3788</td>
<td>2572</td>
<td>NA</td>
</tr>
<tr>
<td>Level 5</td>
<td>MBS 72830</td>
<td>274.15</td>
<td>3</td>
<td>822</td>
<td>558</td>
<td>NA</td>
</tr>
<tr>
<td>Immunohistochemistry</td>
<td>MBS 72846</td>
<td>59.60</td>
<td>1</td>
<td>60</td>
<td>40</td>
<td>NA</td>
</tr>
<tr>
<td>Cytology fine-needle aspiration</td>
<td>MBS 73049</td>
<td>68.15</td>
<td>1</td>
<td>68</td>
<td>46</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Total other procedures</strong></td>
<td></td>
<td></td>
<td>9671</td>
<td>6566</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Total medical procedures (consultations, excisions, monitoring, and other)</strong></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>35 727</td>
<td>24 259</td>
<td>411 278</td>
</tr>
</tbody>
</table>

(continued)
specialists outside the HRC were recorded and topical ointments and lotions were infrequently prescribed (Table 4). Visits for specialist procedures related to the location of the excision or patient preference. Two adverse events (wound infections) were noted in the medical records, and both responded to antibiotics. The mean annual and lifetime costs are summarized in Table 3.

### Table 2. Health System Costs for Patients Attending the HRC During a 12-Month Period (continued)

<table>
<thead>
<tr>
<th>Description</th>
<th>Procedure Code*</th>
<th>Cost per Item, A $ (a)</th>
<th>No. in 12 mo (b)</th>
<th>Total Cost, A $ (c)^d</th>
<th>Cost, US $ (c)^e</th>
<th>Mean Cost per Patient per Year^a</th>
<th>A $ (d)^f</th>
<th>US $ (d)^g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overheads and Capital^i</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office equipment: computers, printers, software and licenses</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3785</td>
<td>2570</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Medical equipment: monitoring, photographic equipment, dermatoscope, lamp, nitrous oxide canister^i</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1298</td>
<td>881</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Consumables, DVDs, gel, stationery, printer toner, gloves, paper rolls, shavers, tissues</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>877</td>
<td>559</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Hospital floor space costs</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2135</td>
<td>1450</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Total overhead</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>8095</td>
<td>5496</td>
<td>31</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Salaries^i,j</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>113605</td>
<td>77133</td>
<td>440</td>
<td>299</td>
<td></td>
</tr>
<tr>
<td>Estimated total medical procedure costs^i</td>
<td></td>
<td></td>
<td></td>
<td>105949</td>
<td>71935</td>
<td>411</td>
<td>279</td>
<td></td>
</tr>
<tr>
<td>Estimated total health system costs</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>227649</td>
<td>154564</td>
<td>882</td>
<td>599</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BCC, basal cell carcinoma; DRG, diagnosis related group; HRC, high-risk clinic; NA, not applicable; SCC, squamous cell carcinoma.

* Unless otherwise indicated, coded as Medicare Benefits Schedule item number for services subsidized by the Australian government.23

* The mean cost per patient was calculated for medical procedures (n=87) based on the microcosting study. The mean capital and salary costs were based on the mean number of patients attending the HRC in a year (n=258).

* Total amount may be less because Medicare Benefits Schedule multiple service rule was applied.23

* Calculated as a × b.

* Calculated as c/n.

* Indicates consultation occurring outside the HRC.

* Australian refined diagnosis-related group classification category.

^a Levels vary according to complexity level of biopsy material being examined, including tissue dissection, preparation, processing, and additional professional opinion(s) that may be sought.

^f Includes 102 patients.

^g Includes costs for recording and storage of lesion images for sequential digital dermoscopy imaging.

^h Includes salaries for the dermatology resident (20 h/wk), administration (17.5 h/wk), research scientist (20 h/wk), clinical supervision (head of department for second opinion and training; 1 h/wk), and information technology support (25 h/y). Salaries have been adjusted to account for Medicare Benefits Schedule fee reimbursement for melanoma surveillance.23

^i Based on extrapolation of medical procedure costs for 87 patients to the estimated 258 patients treated annually at the HRC.

Figure. Distribution of the Cost per Patient Cost to the Health Care System for 12 Months of Surveillance at the High-Risk Clinic

Curve shows the gamma distribution skewing to the right, indicating a small number of people with higher costs. Total mean cost for patients attending the high-risk clinic was A $882 (US $599). The equivalent of US $1 to A $1.47.23
Discussion

The key contributors to the costs of an HRC are labor costs, representing the intensive nature of surveillance, the number of consultations, and the length of time required per patient. The opportunity cost of patients’ time away from work and other activities and the cost of travel are the main drivers for indirect costs.

Recommendations regarding optimal screening (before the diagnosis of melanoma) and surveillance (after the diagnosis) vary within international clinical practice guidelines. Nevertheless, populationscreening is currently not recommended in most countries, some evidence supports follow-up of high-risk groups using an intensive surveillance strategy. Surveillance of high-risk groups is recommended to continue for longer periods because primary melanomas arise at a higher probability than for the general population during these patients’ lifetimes. During the 12-month study period, 34% of the group required an excision of a suspected melanoma lesion and 3 cutaneous melanomas were detected, reflecting the requirement for surveillance.

A systematic review reported significant productivity losses due to the morbidity and premature mortality associated with melanoma. Although progress in the treatment of advanced disease has been made, the mean years of life lost owing to metastatic melanoma are greater compared with other cancers (20.4 vs 16.2 years). This study quantifies the costs of long-term specialized surveillance in a group with a high probability of future melanoma. The 20-year cost of this model is less than that of other well-established surveillance practices for other cancers and compares favorably with surveillance costs in

<table>
<thead>
<tr>
<th>Table 3. Summary of Health System and Societal Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Mean cost per patient per year</td>
</tr>
<tr>
<td>Mean discounted health system cost per patient for 20 years</td>
</tr>
</tbody>
</table>

* The mean cost per patient was calculated for medical procedures (n = 87) based on the microcosting study. The mean capital and salary costs were based on the mean number of patients attending the high-risk clinic in a year (n = 258).

* Mean based on 3.4 visits per person per year because some surveillance and treatment occurs on the same day.

* Australian standard discount rate of 5% has been applied to all future costs.

<table>
<thead>
<tr>
<th>Table 4. Out-of-Pocket Costs for Patients Attending the HRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Medical Costs</td>
</tr>
<tr>
<td>Specialist</td>
</tr>
<tr>
<td>Dermatology consultations</td>
</tr>
<tr>
<td>Dermatology follow-up</td>
</tr>
<tr>
<td>Surgical consultations</td>
</tr>
<tr>
<td>Surgical follow-up</td>
</tr>
<tr>
<td>Theater</td>
</tr>
<tr>
<td>Pharmacy, mean (range)</td>
</tr>
<tr>
<td>Set of total body photographs, annual cost per patient</td>
</tr>
<tr>
<td>Total cost</td>
</tr>
<tr>
<td>Travel Costs, Return Trip</td>
</tr>
<tr>
<td>Car, mean (range)</td>
</tr>
<tr>
<td>Bus, train, or taxi, mean (range)</td>
</tr>
<tr>
<td>Airplane</td>
</tr>
<tr>
<td>Accommodation in Sydney</td>
</tr>
<tr>
<td>Total cost</td>
</tr>
<tr>
<td>Total patient travel costs</td>
</tr>
<tr>
<td>Opportunity Cost of Time Not at Work or Lost Personal Time</td>
</tr>
<tr>
<td>Opportunity cost per visit, mean (range)</td>
</tr>
<tr>
<td>Total cost</td>
</tr>
</tbody>
</table>

Abbreviations: HRC, high-risk clinic; NA, not applicable.

* Calculated as $a \times b$.

* Includes 87 continuing (prevalent) patients.
the United States for early-stage melanoma\textsuperscript{8} (eTable in the Supplement). In addition, a substantial cost advantage is gained if melanoma is treated at an early stage. A study of total health care and societal costs across 5 years based on 2008 Medicare reimbursements in the mid-Atlantic states estimated the cost of managing an in situ melanoma at US $5044 compared with the cost of managing a T4b melanoma at US $110 150.\textsuperscript{8}

The model of care assessed in this study uses specialized expertise to maximize the accuracy of melanoma detection at an early stage and to avoid unnecessary excision of benign lesions. However, costs may be lower using other models of care for high-risk individuals, such as primary care practitioners working in general practice or in skin cancer clinics. Barriers for a general practice setting, such as inadequate time to perform full-body skin examinations\textsuperscript{39} and training in the use of dermoscopy,\textsuperscript{40} would need to be addressed. Research identifying which groups would benefit most from this specialized screening strategy\textsuperscript{41-42} will also improve service efficiency.

A small number of patients had more than 4 excisions within 12 months and some had surgery requiring recovery time, which influences health system and out-of-pocket costs. Hospital admissions would affect health system costs; in our study, however, admission was required for only 1% of patients.

A number of limitations of this study have been identified. Only 1 clinic was observed, and other clinics in different locations may vary in their resource use. Although total costs may differ slightly across clinics for patient management and surveillance, the same protocol recommendations for frequency of skin examination, total body photography, and sequential digital dermoscopic imaging apply to all HRCs in the state; the key contributors to costs we identified would also be applicable in other clinics. Similar principles may be applicable internationally. We did not obtain information from all patients; however, our sample captured consecutive patients whom we believe to be typical of patients attending the clinic. The HRC staff attempted to follow up all reports of excisions performed outside the HRC (eg, by primary care physicians in the community), and these excisions were documented in the medical record. However, a small chance exists that some events may not have been captured. Not all pathologic examination reports were cited; where this occurred, we estimated costs based on the summary reports in the patients’ medical records and therefore may have missed costs for additional histologic stains or expert second opinions that would have been detailed in an original report. In this case, we would be more likely to underestimate rather than overestimate the cost of the pathological examination.

We did not calculate the opportunity cost for 4 accompanying adults in this sample because we could not ascertain whether they attended all consultations during the 12-month study period. Finally, we did not calculate lost work days in terms of lost productivity (business cost) because only 1 person in our study had more than 3 consecutive days off work, and this time off was not considered to have a material effect on the overall results. Further research into valuing patient time\textsuperscript{43} should be considered.

Conclusions

Our study shows that the costs of surveillance for a group of individuals at high risk for melanoma in a specialized HRC can be estimated using microcosting methods. From a health system perspective, the costs of surveillance are driven by the labor costs of the clinic staff and the number of follow-up extended-length surveillance consultations required by these patients. Patients who require more intensive treatment have a greater effect on the overall cost of the program. However, high-risk patients in surveillance programs have been shown to have melanomas detected at an earlier stage compared with high-risk individuals not in a surveillance program.\textsuperscript{4} Costs for their treatment are therefore likely to have been lower than they would have been in standard care. Treatment at an earlier stage also has advantages in terms of decreased morbidity and cost to the community. Calculating costs using a societal perspective further informs the social cost of surveillance in an HRC. In particular, the costs of opportunity foregone and travel reflect the disease burden and the willingness of patients to travel and give up their own time to attend surveillance, indicating the patient's perceived acknowledgment of the benefits of attending the HRC. Results from this study will be used in an economic evaluation of the cost-effectiveness of the specialized HRC model of care for individuals at high risk for melanoma compared with standard care in the community. This study will help to inform health policy for melanoma skin screening and follow-up in Australia.
Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Sharon Lorger, RN, Sydney Medical Diagnostic Center, Sydney Cancer Center, Royal Prince Alfred Hospital, and Ritta Khoury, BMEdSci, Sydney Cancer Centre, Royal Prince Alfred Hospital, assisted with high-risk clinic data collection. No compensation was provided for these contributions.

REFERENCES


Supplementary Online Content


**eMethods.** Health System Costs

**eFigure.** High-Risk Clinic Patients Included in the Microcosting Study

**eTable.** Comparison of Costs for Surveillance Strategies for Individuals at High Risk of Cancer From the Perspective of the Health System

This supplementary material has been provided by the authors to give readers additional information about their work.
**eMethods. Health system costs**

It was assumed that all services provided through the high-risk clinic (HRC) (surveillance and public hospital procedures) and primary care physicians (procedures related to surveillance) were health system costs; ie, that the patient was ‘bulk-billed’ the equivalent of the Medicare Benefits Schedule item number and no out-of-pocket costs were incurred. For patients that were booked to attend during the study period, but had cancelled or did not attend, the date of their most recent visit was taken as the starting date for the 12 month review.

When equipment was used for purposes other than the HRC, a proportion of the total cost was estimated based on the percentage of time it was used by the HRC and an annual cost for equipment was calculated. Based on the mean number of consultations at the HRC in 1 year, a cost per consultation was derived.

There is a health system cost for the medical practitioner for the excision and another for pathology services. The cost of pathology varies with the complexity of the sample being examined. The cost for an excision is dependent on the diagnosis provided by the pathologist, the body site and the number of sites excised in the one visit. Multiple services rules applied for excisions requested within the same visit and are charged at 100% for the first and highest value service, then 50% and 25% cost of subsequent services. Costs were ascertained from original pathology reports and through personal communication with hospital pathology staff.

If there were 3 ‘extended length’ surveillance consultations noted within a calendar year, only the last 2 were included to avoid over-counting consultations which were scheduled at 6 monthly intervals.

**Out-of-pocket and opportunity costs**

Appointment dates and treatment information in patients’ medical records were used to calculate how many trips had been made for surveillance or related procedures and if leave from work had been taken and the time required for the visit. We assumed transport arrangements were consistent over 12 months. For patients who reported travelling by private car, the travel cost to the patient was calculated at the rate for a work-related kilometre at 0.76 cents per kilometre for a standard vehicle with a medium size engine and a parking charge of $6 in the hospital car park was also included. For patients using public transport, travel costs were calculated using the NSW Transport website based on patients reported mode of transport.
travel. If patients were over 60 years it was assumed they were a ‘NSW Seniors Card’ holder and a reduced fare was used. A cost for accommodation was not allocated if patients reported staying with family members.

To ascertain out of pocket costs incurred for visits to private clinicians outside the high risk clinic, a group of dermatology and plastic surgeon clinical practices in Sydney were contacted in order to estimate mean fees and out of pocket costs for these services. Calculation of out of pocket costs was based on the standard reimbursement of the Medicare Benefits Schedule fee.
eFigure. High-risk clinic patients included in the microcosting study

Patients recruited December 2013 to May 2014. Of 102 patients included in the study, 15 were new patients and 87 patients had been attending the clinic for 12 months. Of 87 patients, 67 were directly observed, and 20 patients rescheduled their appointments and had medical record review only.
**eTable 1 Comparison of costs for surveillance strategies for individuals at high risk of cancer from the perspective of the health system**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Target population</th>
<th>Screening intervention</th>
<th>Total cost US$2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang,KY et al (2010)³</td>
<td>Women from Hereditary Non Polyposis Colon Cancer families.</td>
<td>Annual gynecological examination including surveillance using transvaginal ultrasound, endometrial biopsy and serum CA125 testing over a lifetime</td>
<td>US$68,392 $73,066</td>
</tr>
<tr>
<td>Breheny,N et al (2002)⁴</td>
<td>Individuals at risk of Familial Adenomatous Polyposis</td>
<td>Mutation testing, colonoscopy and prophylactic surgery over a lifetime</td>
<td>AUS$90,096 $121,210</td>
</tr>
<tr>
<td>Alexandrescu D et al (2009)⁵</td>
<td>Individuals with a history of Stage 1A melanoma- surveillance only</td>
<td>Dermatology visits and follow-up as per recommendations over 5 years</td>
<td>US$3,759 $4,081</td>
</tr>
<tr>
<td>Present study</td>
<td>Individuals at high risk of melanoma with a history of an invasive melanoma</td>
<td>Dermoscopy, total body photography, and sequential digital dermoscopy imaging and excisions of lesions if morphological change over 5 years.</td>
<td>AUS$4,587 $3,114</td>
</tr>
</tbody>
</table>

**References**


The cost-effectiveness study of the High Risk Clinic

7.1 Preamble

This chapter describes the cost-effectiveness of skin surveillance through a specialised clinic for patients at high risk of melanoma, compared with standard care, from a health system perspective.

Authors
C.G. Watts¹, A.E. Cust¹², S.W. Menzies³, G.J. Mann²⁴, R.L. Morton²⁵

Affiliations
¹ Cancer Epidemiology and Prevention Research, Sydney School of Public Health, The University of Sydney, Sydney, Australia
² Melanoma Institute Australia, The University of Sydney, Sydney, Australia
³ Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital and Dermatology Department, The University of Sydney, Sydney, Australia
⁴ Centre for Cancer Research, Westmead Institute for Medical Research, The University of Sydney, Sydney, Australia
⁵ NHMRC Clinical Trials Centre, The University of Sydney, Sydney, Australia

Funding: CGW and the research study was supported by a PhD scholarship funded through a Cancer Institute NSW fellowship to AEC, a Sydney Catalyst Top-Up Research Scholar Award, and a Cancer Institute NSW Translational Program Grant (10/TPG/1-02) to GJM. RLM was supported by a NHMRC Sidney Sax Fellowship (#1054216). AEC was supported by Career Development Fellowships from the NHMRC (#1063593) and Cancer Institute NSW (#15/CDF/1-14).

Corresponding author:
Caroline Watts
Cancer Epidemiology and Prevention Research, Sydney School of Public Health
7.2 Abstract

Purpose

Clinical guidelines recommend that people at high risk of melanoma receive regular surveillance to improve survival through early detection. A specialised ‘High Risk Clinic’ in Sydney, Australia was found to be effective for this purpose, however wider implementation of this clinical service requires evidence of cost-effectiveness, and data addressing potential over-diagnosis of suspicious skin lesions.

Patients and Methods

A decision-analytic model was built to compare the costs and benefits of a specialised surveillance compared to standard care over a 10-year period, from a health system perspective. A ‘high-risk standard care’ cohort was obtained using linked population data, comprising the Sax Institute’s 45 and Up cohort study, linked to Medicare Benefits Schedule claims data, the cancer registry and hospital admissions data. Benefits were measured in quality-adjusted life years gained. Sensitivity analyses were undertaken for all model parameters.

Results

Specialised surveillance through the High Risk Clinic was both less expensive and more effective than standard care. The mean saving was AUD $6,828 (95% confidence interval (CI) $5,564-$8,092) per patient, and the mean quality-adjusted life year (QALY) gain was 0.31 (95% CI 0.27-0.35). The main drivers of the differences were detection of melanoma at an earlier stage resulting
in less extensive treatment, and a lower annual mean excision rate for suspicious lesions in specialised surveillance (0.81; 95% CI 0.72 to 0.91) compared to standard care (2.55; 95% CI 2.34 to 2.76). The results were consistent when tested in sensitivity analyses.

Conclusion

Specialised surveillance was a cost-effective strategy for the management of individuals at high risk of melanoma. There were also fewer invasive procedures in specialised surveillance compared to standard care in the community.

7.3 Introduction

Melanoma and keratinocytic cancers are the most commonly diagnosed cancers in countries with individuals of predominantly European origin, and their diagnosis and treatment places a high burden on the healthcare system in terms of resource use and costs.\textsuperscript{1-5} Melanoma is less common than keratinocytic cancers but accounts for most skin cancer deaths.\textsuperscript{6} The thickness of a melanoma lesion at diagnosis is an important prognostic marker, and five-year relative survival decreases as thickness increases.\textsuperscript{7} Important risk factors for melanoma, in addition to solar and artificial ultraviolet radiation exposure,\textsuperscript{8} include high melanocytic naevus count and dysplastic naevus syndrome,\textsuperscript{9} a strong family history of melanoma\textsuperscript{10} or high-penetrance gene mutations.\textsuperscript{11} While there is variation in international guidelines about how best to identify and manage high risk patients,\textsuperscript{12} Australian guidelines recommend surveillance intervals that are based on assessment of the level of future risk of melanoma.\textsuperscript{13} Surveillance of patients at high risk of melanoma has been shown to be effective in detecting subsequent melanomas at an early stage.\textsuperscript{14-17}
A High Risk Clinic for patients at high risk of melanoma was established at the Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital, Sydney, Australia, in 2006, to examine the effectiveness of surveillance using digital dermoscopy and total body photography. Assessment of this clinic demonstrated effective surveillance in terms of early detection of melanoma and low excision rates; 91% of melanomas were detected with a lesion thickness less than 1 mm, and the benign to malignant excision ratio for keratinocytic lesions and melanoma was 1.6:1. Monitoring of lesions is time consuming, requires highly trained staff and specific resources. Evidence of cost-effectiveness and data addressing potential over-treatment of suspicious skin lesions is required for wider implementation. This study aimed to address these evidence gaps by conducting a cost-effectiveness analysis from an Australian healthcare system perspective, examining the costs and benefits of skin cancer monitoring using specialised surveillance compared with standard care in the community. Ethical approval was granted by NSW Population and Health Services Research Ethics Committee.

7.4 Patients and methods

7.4.1 Study population of high risk patients

7.4.1.1 Intervention-High Risk Clinic specialised surveillance

High Risk Clinic participants were selected based on having 1) a confirmed family history of three or more first or second degree relatives with melanoma and a confirmed personal history of invasive melanoma, or 2) dysplastic naevus syndrome and a confirmed personal history of invasive melanoma, or 3) a personal history of at least two confirmed invasive melanomas, one diagnosed in the past ten years, or 4) a confirmed high-penetration mutation affecting melanoma risk. Over a five year period, 311 patients underwent specialised surveillance (Table S7.1).
7.4.1.2 Standard Care

A cohort of high risk patients receiving standard (routine) care in the community was identified from The Sax Institute’s 45 and Up cohort study, Australia\textsuperscript{19} linked to population health data from the Medicare Benefits Schedule claims data,\textsuperscript{20} New South Wales Cancer Registry and hospital admissions data from the Admitted Patient Data Collection (online supplementary methods and Figure S1). Patients were selected based on 1) a reported family history of two first degree relatives with melanoma and a confirmed personal history of invasive melanoma, or 2) a personal history of at least two confirmed invasive melanomas, one in the past ten years (Table S7.1). Data was linked using a linkage key provided by the NSW Government’s Centre for Health Record Linkage in accordance with ethical, legal, and confidentiality requirements (online Figure S7.1). Deterministic matching using month and year of melanoma diagnosis, morphology, topography and sex was used to identify and remove 30 patients who were in both standard care and specialised surveillance groups). The standard care group consisted of 607 patients, with data from a similar time-period.

7.4.2 Surveillance-treatment pathway

7.4.2.1 Surveillance

Specialised surveillance for patients attending the High Risk Clinic consisted of two clinic visits per year\textsuperscript{18,21}. If a suspicious lesion was identified, the lesion was excised or the patient was reviewed after three months. The histopathology and classification of all excisions were documented.\textsuperscript{18}
Given their history of invasive melanoma, patients treated with standard care were assumed to undergo an annual skin examination. Australian guidelines recommend that patients with American Joint Cancer Committee (AJCC) stage I melanoma be reviewed at six monthly intervals for the first five years and then annually. Clinical pathways for standard care were obtained through a telephone survey of ten primary care practices in Sydney and major towns in NSW.

7.4.3 Classification and staging of suspicious lesions

Suspicious lesions were categorised into four categories: 1) histopathologically confirmed melanoma; 2) histopathologically confirmed keratinocytic cancers, including basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and SCC in situ; 3) histopathologically confirmed benign lesions; and 4) biopsy of skin or mucous membrane for diagnostic purposes. Excisions were defined based on Medicare Benefit Schedule item numbers pertaining to treatment of suspicious lesions, and included the following procedures: excision, serial curettage, and carbon dioxide laser or erbium laser excision-ablation, including any associated cryotherapy or diathermy (online Table S7.2).

AJCC melanoma staging is based on tumour thickness, ulceration, the number of lymph nodes, nodal metastatic mass, and metastatic spread; however we used a simplified staging classification for both groups because ulceration and mitotic rate were not available from the cancer registry. If spread of disease was not documented, lesion thickness was used to determine stage, defined as in situ (no invasion), pseudo stage I (0-1.0 mm), pseudo stage II (1.01 ≤ 4.00 mm), pseudo stage III (≥ 4.01 mm or lymph node involvement) and pseudo stage IV (distant metastatic disease). We validated the pseudo stage against AJCC stage in all 77 primary melanoma reports from the
specialised surveillance group, and found 92% agreement (and weighted kappa statistic 0.93 CI, 0.87-0.99).

Identification of new primary melanoma and recurrence of melanoma was by histopathology reports in the patients’ medical records (High Risk Clinic) or using cancer registry data (standard care).

7.5 Economic evaluation

7.5.1 Economic methods

A decision-analytic Markov model was developed to simulate the observed management and potential progression of melanoma starting with the identification of a suspicious lesion, observation or treatment, and return to surveillance; or if melanoma, various treatment options based on melanoma stage at diagnosis (online Figures S7.2 and S7.3). The model cycle length was 12-months with a ten year timeframe. There were six health states to represent observed long-term follow-up, informed by comprehensive prognostic and survival data.\(^7\) The economic outcomes were resource use, costs and cost-effectiveness, with the model result reported as the incremental cost per quality-adjusted life year (QALY) gained of specialised surveillance compared to standard care. The Australian standard discount rate of 5%\(^{22}\) was applied to all future costs and benefits. All costs were adjusted to 2013 dollars using published deflators.\(^{23}\) The Markov model was constructed using TreeAge Pro 2015, and statistical analysis performed using SAS 9.4 (SAS Institute Inc). The analysis was reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement\(^{24}\) checklist.
7.5.2 Resource use and costs

7.5.2.1 High Risk Clinic

Resource use, costs and clinical pathways for specialised surveillance were estimated using published data from the High Risk Clinic\textsuperscript{18,21} (Table 7.1). Unit costs for melanoma, keratinocytic and benign lesion excisions were obtained from the appropriate Medicare Benefits Schedule\textsuperscript{20} item numbers, and our micro-costing study\textsuperscript{21} (Table 7.2). Cryotherapy rates were estimated from High Risk Clinic billing records from June 2013 to June 2015 and re-excision of keratinocytic lesions from standard care data. As the High Risk Clinic operates within a public hospital, the standard fee for service is 85\% of the scheduled fee.\textsuperscript{25}

7.5.2.2 Standard care

The standard care linked dataset (2006-2010) was used to calculate the frequency of procedures by lesion type. We used Medicare Benefits Schedule item numbers to calculate the cost of excisions, using a weighted average based on the size and anatomical location of the lesion and procedure (Table 7.1 and Table 7.2). For services provided outside a hospital, costs were calculated at 100\% of the schedule fee.

The multiple service rule\textsuperscript{20} was applied when multiple excision types resulted in a reduced cost for second and subsequent excisions (50\% and 25\% respectively) and pathology costs (Table 7.2).
7.5.2.3 Hospital costs

Costs for hospital treatment (Table 7.2) were obtained from Admitted Patient Data Collection hospital admission ICD-10 diagnosis codes for melanoma linked to the cancer registry using stage and year of diagnosis. Mean costs by stage at diagnosis were calculated using Australian-Refined Diagnosis Related Group\textsuperscript{22} classifications (online Table S7.3) and length of stay in hospital. The cost of a wide excision was calculated as the mean hospital cost, based on patients with in situ or stage I melanoma. The cost of a sentinel lymph node biopsy was calculated as the mean cost of stage II admissions minus the mean cost of a wide excision (online Table S4). Stage III costs were estimated from ICD-10 admission and treatment codes for lymph node dissection and Medicare Benefits Schedule data for relevant treatment and follow-up (online supplementary methods and Figure S7.4). Costs for ongoing surveillance were based on the predicted frequency of specialist consultations.\textsuperscript{13} Costs related to death in hospital,\textsuperscript{26} palliative care\textsuperscript{27,28} and treatment for metastatic disease\textsuperscript{29,30} were obtained from published sources.

7.5.3 Model transitions

For specialised surveillance, the probability of melanoma by stage at diagnosis and the annual frequency of excisions by lesion type was obtained from the High Risk Clinic five year follow-up study\textsuperscript{18} (Table 7.1 and Table S7.5). High Risk Clinic participants joined the study at different time points. For our analysis, all patients started the model in their first year of surveillance. Data for all 311 participants were included.

Cancer registry data from 2004-2008 were used to calculate the probability of melanoma by stage at diagnosis, and linked with the Medicare Benefits Schedule (years 2006-2008) to calculate the
probability of excision by lesion type and to exclude excisions due to recurrence (Table 7.1 & Table S7.5). Survival estimates for the general population were obtained from life-tables of the Australian Bureau of Statistics\textsuperscript{31} and for melanoma-specific deaths from AJCC staging estimates\textsuperscript{7} (Table 7.1).

### 7.5.4 Quality of life scores and utilities

Utility values were assigned to health states. These utilities reflect society’s valuation of health states under conditions of uncertainty ranging from 1.0 for full health to zero for death.\textsuperscript{32} Utilities for melanoma were obtained from a prospective study of melanoma patients that measured health states longitudinally by stage at diagnosis and at remission.\textsuperscript{33} Utilities for excisions of non-melanoma skin cancer,\textsuperscript{34} benign naevus and keratinocytic lesions were sourced from published literature (Table 7.2).\textsuperscript{35} Individuals without an excision were assumed to be in full health.

### 7.5.5 Sensitivity analyses

A series of one-way and two-way sensitivity analyses were performed to test the strength of the conclusions of the model and to test the model parameters. Where high and low estimates could not be obtained from the literature, we used a standard multiplier formula (0.5-2.0) to address sensitivity around our model parameters. Quality of life measures were tested using 95% confidence intervals (CI). For two-way sensitivity analyses, we examined each parameter separately for an effect on the ratio of costs and outcomes. For probabilistic sensitivity analysis, we performed a Monte Carlo simulation, sampling 1,500 times from randomly assigned distributions of key variables identified from our one-way sensitivity analysis. We used beta
distributions for all probabilities and utility values and gamma distributions for cost parameters (Table S7.6). The baseline values, ranges and distributions are shown in Tables 7.1 and 7.2.

7.6 Results

Specialised surveillance was both less expensive and more effective than standard care. The mean saving was AUD $6,828 (95% CI $5,564-$9,029) per patient and the mean QALY gain was 0.31 (95% CI 0.27-0.35) for patients in specialised surveillance compared to standard care. The results for the base case are shown in Table 7.3. The mean cost per patient over ten years in specialised surveillance was AUD $13,468 and in standard care was AUD $20,296; the QALYs were 7.87 and 7.56, respectively. The main drivers for these differences were detection of melanoma at an earlier stage resulting in lower treatment costs, and fewer excisions for suspicious lesions in specialised surveillance compared to standard care. The annual probability of an excision was lower in specialised surveillance (0.40; 95% CI 0.33-0.46) compared to standard care (0.64; 95% CI 0.61-0.68). This corresponded to an annual mean number of excisions for suspicious lesions of 0.81 (95% CI 0.72 to 0.91) in specialised surveillance and 2.55 (95% CI 2.34 to 2.76) in standard care. Among patients who had at least one excision, the mean number of excisions over a 12 month period remained lower in specialised surveillance (2.05; 95% CI 1.93 to 2.219) than in standard care (3.98; 95% CI 3.82 to 4.14) (Table 7.4).


7.6.1 Sensitivity analyses

The results of one-way sensitivity analyses indicated that the variables most likely to influence the incremental cost-effectiveness ratio were the probability of an excision in standard care and specialised surveillance, the annual cost of specialised surveillance, and the cost of treating metastatic disease. A tornado diagram (online Figure S7.5) shows the variables with the greatest influence on the results stacked at the top of the graph. A low probability of excision in the standard care arm was the only variable observed to increase the incremental cost-effectiveness ratio above a willingness to pay of $50,000 per QALY; and would need to be less than 0.32 to be the cost-effective strategy (Figure 7.1). Probabilistic sensitivity analysis showed the incremental costs and quality-adjusted survival points predominantly in the bottom right quadrant of the cost-effectiveness plane (Figure 7.2), indicating that specialised surveillance is a less costly and more effective strategy.

7.7 Discussion

Providing appropriate surveillance for patients at higher risk of melanoma is the key focus of skin cancer screening and has been shown to be effective in detecting subsequent melanomas at an early stage. We found that specialised surveillance was a cost-effective strategy for the management of individuals at high risk of melanoma. Specialised surveillance was less expensive and more effective compared to standard care, primarily because melanoma was detected at an earlier stage and there were fewer excisions performed.

Data were only included in our study if available for both specialised surveillance and standard care groups. Access to linked population datasets including Medicare claims, cancer registry and
hospital data allowed us to accurately measure health system expenditure for a standard care comparator group over a similar time-period to the High Risk Clinic follow-up study. Complete data were available for melanoma excisions and hospitalisations, and for keratinocytic lesion excisions. However, a limitation of our study is that hospitalisation costs were not able to be included for keratinocytic lesions because these data were not available for High Risk Clinic participants. We estimated keratinocytic lesion re-excisions for specialised surveillance based on Medicare Benefits Schedule data, where they represented less than 2% of excisions. In 2008, 61% of total expenditure on keratinocytic lesions was for out-of-hospital care and 36% was for admitted care.\textsuperscript{38} In our Markov model, we assumed that skin examinations were conducted annually in standard care and biannually in specialised surveillance. Because patients in standard care had more excisions, it is possible that we have underestimated the number of clinician appointments and therefore underestimated the cost of surveillance in standard care.

Although the standard care group was not a randomised control arm, we aimed to ‘match’ the risk factor profile for the standard care group to that for High Risk Clinic participants. As a result, there were some differences in baseline characteristics because the groups could not be matched perfectly. On the one hand, High Risk Clinic participants may have had higher-risk characteristics because their family history data were confirmed, whereas the linked dataset for standard care was based on self-reported family history. On the other hand, the standard care group had a higher proportion of men, and on average were slightly older and of lower socio-economic status than the High Risk Clinic group. These are considered higher-risk characteristics because lower educational attainment, male gender and older age have been linked to more advanced melanoma in Australia,\textsuperscript{39} and risk of melanoma and keratinocytic cancer increases with age.\textsuperscript{1} Data for dysplastic naevus syndrome were not available for the linked dataset so that risk factor could not
be compared. Although the cancer registry data did not contain AJCC staging information, the pseudo stage used to classify all melanoma reports was found to have high agreement when validated against the AJCC stage classifications for primary melanomas detected in the High Risk Clinic.

Our study highlights several areas for further research. Our data on excisions indicate that there were fewer invasive procedures in specialised surveillance compared to the community. There are several factors influencing treatment and whether a doctor would excise or take a ‘watch and wait’ approach to a suspicious lesion, including level of training, the desire not to misdiagnose, patient pressure, time and work constraints for both the clinician and patient, and a fee-for-service payment system.\textsuperscript{40-42} Other aspects of surveillance that should be examined include assessment of societal costs (e.g. patient out-of-pocket costs for travel, specialist visits or treatment; productivity losses), patient satisfaction, and adherence to a surveillance regimen. Our micro-costing study reported societal costs of attending the High Risk Clinic were similar to health system costs, largely due to the considerable time commitment of patients to attend the clinic. The High Risk Clinic in this study was located at a major, city-based hospital. It would be useful to model the costs and benefits of specialised surveillance in alternative settings, for example in primary care settings (e.g. skin cancer clinics) or specialist dermatology practices.

Further exploration of risk factors may help to identify patients who require less intensive surveillance, as not all patients had a lesion excised over the study period. For some cancers, a less intensive follow-up program has been shown to be the most cost-effective approach.\textsuperscript{43} However, our findings indicate that for high-risk patients managed with specialised surveillance, rather than contributing to over-treatment, surveillance with a careful ‘watch and wait’ approach...
to suspicious skin lesions resulted in fewer excisions and lower costs compared to surveillance in the community.

Acknowledgments: We would like to thank Sharon Lorger and Ritta Khoury for assisting with providing relevant cost data from the High Risk Clinic. Denise Stavrianos for pathology coding information. The Commonwealth Department of Human Services supplied the Medicare Benefits Schedule claims data to the Sax Institute. This research was completed using data collected through the 45 and Up Study (www.saxinstitute.org.au). The 45 and Up Study is managed by the Sax Institute in collaboration with major partner Cancer Council NSW; and partners: the National Heart Foundation of Australia (NSW Division); NSW Ministry of Health; NSW Government Family & Community Services – Carers, Ageing and Disability Inclusion; and the Australian Red Cross Blood Service. We thank the many thousands of people participating in the 45 and Up Study and staff from The Centre for Health Record Linkage, NSW Cancer Registry, The 45 and Up Study and NSW Health Department, for assistance with data linkage.
7.8 References

References


### Table 7.1. Model inputs for High Risk Clinic (specialised surveillance), and Standard care treatment strategies

<table>
<thead>
<tr>
<th>Item</th>
<th>Specialised surveillance</th>
<th>Standard care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base case</td>
<td>Low$^a$</td>
</tr>
<tr>
<td><strong>Annual probabilities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma by stage at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insitu melanoma</td>
<td>0.45</td>
<td>0.02</td>
</tr>
<tr>
<td>Stage I melanoma</td>
<td>0.42</td>
<td>0.02</td>
</tr>
<tr>
<td>Stage II melanoma</td>
<td>0.09</td>
<td>0.04</td>
</tr>
<tr>
<td>Stage III melanoma</td>
<td>0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>Stage IV melanoma</td>
<td>0.000</td>
<td>na</td>
</tr>
<tr>
<td><strong>Excisions under surveillance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of an excision</td>
<td>0.40</td>
<td>0.21</td>
</tr>
<tr>
<td>Melanoma only</td>
<td>0.12</td>
<td>0.06</td>
</tr>
<tr>
<td>Keratinocytic lesion only</td>
<td>0.18</td>
<td>0.09</td>
</tr>
<tr>
<td>Benign lesions only</td>
<td>0.50</td>
<td>0.25</td>
</tr>
<tr>
<td>Melanoma &amp; keratinocytic lesion</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Melanoma &amp; benign lesion</td>
<td>0.07</td>
<td>0.03</td>
</tr>
<tr>
<td>Keratinocytic &amp; benign lesion</td>
<td>0.09</td>
<td>0.04</td>
</tr>
<tr>
<td>Melanoma &amp; keratinocytic &amp; benign lesion</td>
<td>0.01</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Event rates for hospital treatment by stage of disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of receiving a sentinel lymph node biopsy procedure</td>
<td>0.72</td>
<td>0.36</td>
</tr>
<tr>
<td>Probability of sentinel lymph node biopsy being positive</td>
<td>0.13</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Stage III and stage IV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease free 5 year survival stage III</td>
<td>0.62</td>
<td>0.47</td>
</tr>
<tr>
<td>Probability of progression to stage IV</td>
<td>0.28</td>
<td>0.14</td>
</tr>
<tr>
<td>Relapse in stage III</td>
<td>0.50</td>
<td>0.25</td>
</tr>
<tr>
<td>Probability of resectable disease (over 2 yrs)</td>
<td>0.48</td>
<td>0.25</td>
</tr>
<tr>
<td>5 year survival with stage III relapse and potentially resectable disease (early detection of metastases)</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>5 year survival with stage III relapse and potentially unresectable disease (late detection of metastases)</td>
<td>0.18</td>
<td>0.09</td>
</tr>
<tr>
<td>Disease free 5 year survival Stage IV</td>
<td>0.18</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Utilities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full health</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Insitu melanoma- treatment</td>
<td>0.687</td>
<td>0.642</td>
</tr>
<tr>
<td>Insitu melanoma- remission</td>
<td>0.809</td>
<td>0.773</td>
</tr>
<tr>
<td>Stage I melanoma- treatment</td>
<td>0.579</td>
<td>0.642</td>
</tr>
<tr>
<td>Stage I melanoma- remission</td>
<td>0.802</td>
<td>0.773</td>
</tr>
<tr>
<td>Stage II melanoma- treatment</td>
<td>0.579</td>
<td>0.486</td>
</tr>
<tr>
<td>Stage II melanoma- remission</td>
<td>0.802</td>
<td>0.764</td>
</tr>
<tr>
<td>Stage III melanoma- treatment</td>
<td>0.535</td>
<td>0.395</td>
</tr>
<tr>
<td>Stage III melanoma- remission</td>
<td>0.703</td>
<td>0.659</td>
</tr>
<tr>
<td>Procedure</td>
<td>Probability</td>
<td>Probability</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Stage IV melanoma- treatment</td>
<td>0.583</td>
<td>0.524</td>
</tr>
<tr>
<td>Stage IV melanoma- remission</td>
<td>0.796</td>
<td>0.708</td>
</tr>
<tr>
<td>Keratinocytic lesion excision</td>
<td>0.976</td>
<td>0.924</td>
</tr>
<tr>
<td>Benign naevus excision</td>
<td>0.971</td>
<td>0.924</td>
</tr>
</tbody>
</table>

* Calculation for sensitivity analyses based on multiplier formula (0.5 and 2) for excision probabilities and from published literature for other values.

Pseudo-stage based on Breslow thickness (see Methods). Based on data used for the High Risk Clinic study.

Pseudo-stage based on Breslow thickness if degree of spread not provided, using linked data from The Sax Institute’s 45 and Up study, with Medicare Benefits Schedule and NSW Cancer Registry 2006-2008 data.

Calculations for probabilities by lesion type as determined by the model structure (see online Table S5). Probabilities exclude excisions for melanoma recurrence and MBS item no 30071 (Diagnostic incision/shave biopsy of skin or mucous membrane).

Linked data from The Sax Institute’s 45 and Up study with Medicare Benefits Schedule 2006-2010 and NSW Cancer Registry data.
Table 7.2. Summary of annual costs in the specialised surveillance and in standard care

<table>
<thead>
<tr>
<th>Description</th>
<th>Annual base case</th>
<th>Range(^a)</th>
<th>Medicare Benefits Schedule/ Source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUD$</td>
<td>Low AUD$</td>
<td>High AUD$</td>
</tr>
<tr>
<td><strong>Specialised surveillance(^b)</strong></td>
<td>884</td>
<td>884</td>
<td>1,022</td>
</tr>
<tr>
<td><strong>Specialised surveillance excisions(^c,d)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma excision biopsy(^e)</td>
<td>453</td>
<td>227</td>
<td>906</td>
</tr>
<tr>
<td>Keratinocytic lesion(^g)</td>
<td>268</td>
<td>128</td>
<td>511</td>
</tr>
<tr>
<td>Benign lesion(^g)</td>
<td>204</td>
<td>96</td>
<td>383</td>
</tr>
<tr>
<td>Melanoma excision biopsy(^e) &amp; keratinocytic</td>
<td>563</td>
<td>293</td>
<td>1173</td>
</tr>
<tr>
<td>lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma excision biopsy(^e) &amp; benign lesion</td>
<td>484</td>
<td>261</td>
<td>1045</td>
</tr>
<tr>
<td>Keratinocytic &amp; benign lesion</td>
<td>308</td>
<td>173</td>
<td>691</td>
</tr>
<tr>
<td>Melanoma excision biopsy(^e) &amp; keratinocytic &amp;</td>
<td>579</td>
<td>334</td>
<td>1336</td>
</tr>
<tr>
<td>benign lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incision/shave biopsy(^f)</td>
<td>44</td>
<td>22</td>
<td>89</td>
</tr>
<tr>
<td><strong>Standard care surveillance(^h)</strong></td>
<td>70</td>
<td>70</td>
<td>140</td>
</tr>
<tr>
<td><strong>Standard care excisions(^d,i)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma excision biopsy(^e) i</td>
<td>463</td>
<td>232</td>
<td>926</td>
</tr>
<tr>
<td>Keratinocytic lesion(^k)</td>
<td>260</td>
<td>129</td>
<td>514</td>
</tr>
</tbody>
</table>

\(^a\) MBS item 23, High Risk Clinic surveillance costs $744

\(^b\) MBS items 72830, 23, 110, 73924, weighted cost for excision MBS item 31205 & 31210

\(^c\) MBS items 72816, 23, 73924, weighted cost for keratinocytic lesion excision $171

\(^d\) MBS items 72816, 23, 73924, weighted cost for benign lesion excision $94 as above; multiple service rule applied to excisions, pathology MBS item 72830

\(^e\) MBS items 72816, 23, 73924, weighted cost for keratinocytic lesion excision $171

\(^f\) MBS items 72817 or 72818

\(^g\) MBS items 72816, 23, 73924, weighted cost for benign lesion excision $94 as above; multiple service rule applied to excisions, pathology MBS item 72830

\(^h\) MBS item 23

\(^i\) MBS items 72830, 110, 73927, weighted cost for excision MBS item 31205 & 31210

\(^j\) MBS items 72816, 73927, weighted cost for keratinocytic lesion excision $171
### Calculation for sensitivity analyses based on multiplier formula (0.5 and 2) for excision probabilities and from published literature for other values.

### Based on mean annual cost from micro-costing study:
- Total Body Photography ($34), sequential digital dermoscopy ($65), and two extended appointments for skin surveillance ($140), and mean annual salary and overheads of High Risk Clinic ($645).

### High Risk clinic excision data were based on results from a 5-year review of the High Risk Clinic. All excisions were classified by lesion type.

### Hospital costs

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Cost 0.5</th>
<th>Cost 1.0</th>
<th>Cost 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wide excision</td>
<td>2,974</td>
<td>2,416</td>
<td>3,533</td>
</tr>
<tr>
<td>Sentinel lymph node biopsy</td>
<td>2,686</td>
<td>1,167</td>
<td>4,205</td>
</tr>
<tr>
<td>Complete lymph node dissection</td>
<td>11,492</td>
<td>8,450</td>
<td>14,797</td>
</tr>
<tr>
<td>Treatment for recurrent stage III or stage IV</td>
<td>125,239</td>
<td>94,480</td>
<td>156,120</td>
</tr>
</tbody>
</table>

### Stage III monitoring costs

<table>
<thead>
<tr>
<th>Stage III year</th>
<th>Cost 0.5</th>
<th>Cost 1.0</th>
<th>Cost 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 2</td>
<td>2,127</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 3</td>
<td>1,813</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 4</td>
<td>1,813</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 5</td>
<td>157</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years 6 to 10</td>
<td>157</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Other costs

<table>
<thead>
<tr>
<th>Service</th>
<th>Cost 0.5</th>
<th>Cost 1.0</th>
<th>Cost 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palliative care</td>
<td>22,092</td>
<td>11,046</td>
<td>44,184</td>
</tr>
<tr>
<td>End of life care</td>
<td>17,714</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### MBS items
- 72816, 73927, weighted cost for benign lesion excision $63
- 72830, weighted cost for excision biopsy $72830
- 72817 or 72818, weighted cost for multiple service rule applied to excisions
- 30071, weighted cost for high risk clinic excision

### PET: positron emission tomography; MBS: Medicare Benefits Schedule

---

1 Calculation for sensitivity analyses based on multiplier formula (0.5 and 2) for excision probabilities and from published literature for other values.
2 Based on mean annual cost from micro-costing study: Total Body Photography ($34), sequential digital dermoscopy ($65), and two extended appointments for skin surveillance ($140), and mean annual salary and overheads of High Risk Clinic ($645).
3 High Risk clinic excision data were based on results from a 5-year review of the High Risk Clinic. All excisions were classified by lesion type.
Mean cost for an excision. Patients may have more than one excision in a year. The base case assumes all excisions take place at the time of a skin examination. Procedures within a hospital were costed at 85%, or if outside a hospital at 100%. The multiple service rule was applied for multiple excision types on the same day. Pathology costs were valued as Level 5 (Medicare Benefits Schedule item 30195) for melanoma reports or level 3 (Medicare Benefits Schedule item 72823) for keratinocytic and benign naevus reports, based on personal communication with pathology staff at Royal Prince Alfred Hospital. One annual pathology cost was levied if a patient had an excision. If melanoma was reported MBS item no 72830 was used, otherwise MBS item 72816, 72817 or 72818 was used dependant on number of annual excisions. One pathology handling fee per patient was included; MBS item 73924 for High Risk Clinic patients and 73927 for standard care patients. For the purposes of this analysis, a wide excision was assumed to be performed in hospital and was included under hospital costs.

Weighted mean cost for melanoma excision biopsy from the linked data set using Medicare Benefits Schedule item numbers 31205-31210. Contains an additional costs for suture removal outside the hospital and referral to a specialist surgeon for a wide excision.

Incision biopsy pathology cost was bundled under other the pathology item number for excisions done at the same time.

Weighted mean cost based on medical records of keratinocytic and benign lesion excisions for 87 High Risk Clinic patients over a 12-month period.

Based on costs for a clinical appointment for a skin examination from a primary care physician, based on a telephone survey of skin cancer clinics and mixed practice clinics in NSW.

Standard care group excision data were calculated from a linked data using The Sax Institute’s 45 and Up study with data from the Medicare Benefits Schedule, NSW Cancer Registry, and NSW Admitted Patient Data Collection 2006-2010.

Contains an additional cost for referral to specialist surgeon for a wide excision.

Weighted mean cost for keratinocytic and benign lesions excisions from Medicare Benefits Schedule item numbers used by the standard care group (online supplementary Table S2).

Hospital costs have been calculated using linked data from the NSW Cancer Registry and the Admitted Patient Data Collection (online supplementary Table S3 and Table S4).

Based on a follow-up schedule of four patient review appointments in year 2, two reviews in Year 3 and 4, and one review thereafter using ultrasound and positron emission tomography (PET). PET is not continued after 4 years.
Table 7.3. Mean total costs (A$) and QALYs per patient over 10 years for each strategy

<table>
<thead>
<tr>
<th></th>
<th>Specialised surveillance</th>
<th>Standard care</th>
<th>Difference (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean cost per patient</td>
<td>$13,468</td>
<td>$20,295</td>
<td>$6,828 ($5,564-$8,092)</td>
</tr>
<tr>
<td>QALYs(^a)</td>
<td>7.87</td>
<td>7.56</td>
<td>0.31 (0.27-0.35)</td>
</tr>
</tbody>
</table>

\(^a\) Quality-adjusted life years
Table 7.4. Mean excisions per person in specialised surveillance and standard care from 2006-2010

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients</th>
<th>Total patients</th>
<th>Probability of an excision</th>
<th>All excisions</th>
<th>Mean number excisions per person</th>
<th>Mean number excisions per person with an excision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>311</td>
<td>133</td>
<td>0.43</td>
<td>275</td>
<td>0.88</td>
<td>2.07</td>
</tr>
<tr>
<td>2</td>
<td>280</td>
<td>127</td>
<td>0.45</td>
<td>256</td>
<td>0.91</td>
<td>2.02</td>
</tr>
<tr>
<td>3</td>
<td>257</td>
<td>98</td>
<td>0.38</td>
<td>189</td>
<td>0.74</td>
<td>1.93</td>
</tr>
<tr>
<td>4</td>
<td>197</td>
<td>56</td>
<td>0.28</td>
<td>130</td>
<td>0.66</td>
<td>2.32</td>
</tr>
<tr>
<td>5</td>
<td>97</td>
<td>40</td>
<td>0.41</td>
<td>84</td>
<td>0.87</td>
<td>2.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.40</td>
<td>0.81</td>
<td>2.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients</th>
<th>Total patients</th>
<th>Probability of an excision</th>
<th>All excisions</th>
<th>Mean number excisions per person</th>
<th>Mean number excisions per person with an excision</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.64</td>
<td>0.61</td>
<td>2.30</td>
</tr>
</tbody>
</table>

Weighted over 5 years

* Surveillance years based on calendar year for standard care patients and years under surveillance for High Risk Clinic patients where all patients start surveillance at day 1 but have joined the study at different time points. Hence not all High Risk Clinic patients will have 5 years surveillance.

* Includes patients who had an excision biopsy, pathology confirmed melanoma, keratinocytic or benign lesion during study period.

* Total excisions includes excisions biopsy and pathology confirmed melanoma, keratinocytic or benign lesion.
**Figure 7.1.** Two-way sensitivity analysis for the probability of an excision in specialized surveillance compared with probability of excision in standard care. At a willingness to pay of AUD$50,000 per QALY, specialized surveillance is cost-effective compared to standard care. X indicates the base case intersection point of the probability of excision in specialized surveillance of 0.40 and the probability of excision in standard care of 0.64. (See Table 1) The probability of an excision in standard care would need to be below 0.32 (shown as O) for standard care to be the cost-effective surveillance option.
Figure 7.2. Incremental cost-effectiveness, specialised surveillance v. standard care. Estimated joint cost-effectiveness density for the specialised surveillance model presented on a cost-effectiveness plane. The ellipse represents the 95% confidence interval of joint cost and effect pairs from Monte Carlo simulation. The majority of cost and effect pairs fall below the willingness to pay (WTP) line of $50,000 per QALY and within the bottom right quadrant of the cost-effectiveness plane, indicating with reasonable certainty that the specialised surveillance strategy is both more effective and less expensive than standard care.
7.10 Supplementary materials

Supplementary Methods

Description of data sets for linked data

The 45 and Up study

The Sax Institute’s 45 and Up Study is a population-based study of over 267,000 residents aged over 45 years from New South Wales, Australia, randomly sampled from the Department of Human Services (formerly Medicare Australia) database. Following recruitment between January 2006 and December 2009, participants completed a baseline questionnaire that included questions about their personal and family history of melanoma and gave signed consent for follow-up and linkage of their information to a range of health databases. The first follow-up of participants began in 2012, and will continue over the next few years. The response rate to the Study was about 18%, similar to other studies requiring extensive consent for data linkage. While there may be a “healthy cohort effect” due to the sampling method requiring the completion of questionnaires, the 45 and Up Study is unique because of the potential for ongoing linkage.

Department of Human Services- Medicare Benefits Schedule (2003-2011)

The Department of Human Services processes patient claims for medical services that are subsidised by the Australian government. Services covered under the Medicare Benefits Schedule include consultations with general practitioners and specialists, some nursing and allied health care and diagnostic services. All claims processed have a patient identifier number, a service provider identifier number, the date of service, the Medicare Benefits Schedule item number, provider speciality and specialty group to identify the type of service provided, which we utilised for this study. There is currently no MBS item...
number for a full body skin examination. All patients who had seen a general practitioner in the year of interest were assumed to be under surveillance. A conservative estimate of one skin examination per year was made to estimate the costs of patients undergoing standard care surveillance.

*New South Wales Health Department- Admitted Patient Data Collection (2005-2011)*

The admitted patient dataset contains a record of all inpatient episodes from public, private and repatriation hospitals, private day procedures centres and public nursing homes in NSW. Data included dates of admission and discharge, principle diagnoses and clinical information (based on the International Classification of Diseases, using the 10th revision Australian modification CD-10-AM), procedures (classified using Medicare Benefits Schedule item number derived classifications), and Australian Refined Diagnostic Related Groups (AR-DRGs).²

*NSW Cancer Registry (1994-2008)*

The New South Wales Cancer Registry records cancer diagnoses reportable by law for residents of New South Wales and the Australian Capital Territory. Reports included all New South Wales residents with a histopathologically confirmed primary in situ or invasive cutaneous or unknown primary site melanoma (ICD-O-3 site codes C44.0 to C44.9 and C80.9; morphology codes 8720-8790 /0 /2 or /3).³ The data included both first reported invasive melanoma and subsequent melanoma reports. Additional data included Breslow depth (thickness of lesion), body site location, description of cancer spread from the point of origin at the time of diagnosis, month and year of diagnosis. For subsequent reports of melanoma, degree of spread and Breslow thickness was generally less detailed.
Selection of the standard care group

Questionnaire items from the 45 and Up Study that were used in this study included: age, sex, department of veteran affairs status, and personal and family history of melanoma. The standard care group was selected following linkage with Cancer Registry data and based on 1) a confirmed history of an invasive melanoma and questionnaire data from the 45 and Up Study reporting two first degree relatives with a history of melanoma or 2) a confirmed history of two invasive melanomas, one diagnosed between 1999-2008.

Ethical approvals

Approval for the study was granted by the NSW Population and Health Services Research Ethics Committee based on prior approvals for access and provision of a linkage key by the Centre for Health Record Linkage (CHeReL) for the Cancer Registry data and the Admitted Patient Data Collection from the respective data custodians. Approval for data access and linkage key by the CHeReL for The 45 and Up Study and Medicare Benefits Schedule data was obtained from the Sax Institute’s Data Access Committee.

Estimating hospital and follow-up costs for year of diagnosis of Stage III melanoma

Following initial diagnosis of a melanoma, published data indicated that surgical management, including sentinel lymph node biopsy, would be based on clinical practice guidelines relating to tumour depth and hence hospital costs would not differ between the two groups for a melanoma of the same thickness and site. Data from the Admitted Patient Data Collection was used to estimate the costs of hospitalization. Patients who had an admission ICD-10 diagnosis code with melanoma as a primary reason for admission, and a Medicare Benefits Schedule episode code indicating a lymph node dissection (30330-00,
30336-00, 31435-00, 31438-00 or 90282-00, 90282-01, 90282-02) were used to estimating hospital costs for Stage III melanoma. If individuals had more than one admission in the year, the first admission only was used to estimate the mean cost. To estimate the annual mean cost (calculated from the date of admission to hospital), costs for follow-up following discharge were calculated from the date of discharge. Patient records from the Admitted Patient Data Collection used to estimate hospital costs were linked to the Medicare Benefits Schedule. A matrix was constructed to select probable treatment related to follow-up using Medicare Benefits Schedule item numbers for staging, treatment and pathology (Table S7.1) and data in the Admitted Patient Data Collection with the relevant provider speciality and speciality groups (Figure S7.4) as appropriate to Stage III management. Individual patient costs were calculated from the date of hospital discharge to 12 months from the admission date. Costs for all years were adjusted using deflators to 2103 costs. Mean costs for hospitalization and follow-up were added to calculate the mean annual cost of Stage III treatment following diagnosis.

References


**Table S7.1.** Characteristics of patients in High Risk Clinic undergoing specialised surveillance and in standard care groups

<table>
<thead>
<tr>
<th></th>
<th>High Risk Clinic</th>
<th>Standard Carea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=311</td>
<td>n=607</td>
</tr>
<tr>
<td></td>
<td>n (%) or median (IQR)</td>
<td>n (%) or median (IQR)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>179 (58)</td>
<td>402 (66)</td>
</tr>
<tr>
<td>Females</td>
<td>132 (42)</td>
<td>205 (33)</td>
</tr>
<tr>
<td>Age in 2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males, median (IQR)</td>
<td>58 (50-67)</td>
<td>68 (60-76)</td>
</tr>
<tr>
<td>Females, median (IQR)</td>
<td>50 (41-58)</td>
<td>60 (50-68)</td>
</tr>
<tr>
<td>Patient characteristicsb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family historyc and personal history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple primary melanomasd</td>
<td>146 (47)</td>
<td>514 (85)</td>
</tr>
<tr>
<td>Naevi and history of melanoma</td>
<td>219 (70)</td>
<td>Unable to ascertain</td>
</tr>
<tr>
<td>CDKN2A mutation</td>
<td>17 (5)</td>
<td></td>
</tr>
<tr>
<td>Index of Relative Socio-Economic Disadvantagee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st quintile (most disadvantaged)</td>
<td>24 (8)</td>
<td>95 (16)</td>
</tr>
<tr>
<td>2nd quintile</td>
<td>43 (14)</td>
<td>135 (22)</td>
</tr>
<tr>
<td>3rd quintile</td>
<td>55 (18)</td>
<td>125 (21)</td>
</tr>
<tr>
<td>4th quintile</td>
<td>46 (15)</td>
<td>89 (15)</td>
</tr>
<tr>
<td>5th quintile (least disadvantaged)</td>
<td>143 (46)</td>
<td>136 (22)</td>
</tr>
<tr>
<td>Unrecorded</td>
<td>n/a</td>
<td>27 (4)</td>
</tr>
<tr>
<td>Characteristics of last melanoma prior to 2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breslow depth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insitu</td>
<td>62 (20)</td>
<td>26 (5)</td>
</tr>
<tr>
<td>0.01-1.00 mm</td>
<td>175 (56)</td>
<td>334 (6)</td>
</tr>
<tr>
<td>1.01-2.00 mm</td>
<td>26 (8)</td>
<td>96 (17)</td>
</tr>
<tr>
<td>2.01-4.00 mm</td>
<td>22 (7)</td>
<td>35 (6)</td>
</tr>
<tr>
<td>&gt;4.00 mm</td>
<td>13 (4)</td>
<td>16 (3)</td>
</tr>
<tr>
<td>Unrecorded</td>
<td>13(4)</td>
<td>49 (9)</td>
</tr>
<tr>
<td>No previous melanoma f</td>
<td>n/a</td>
<td>51</td>
</tr>
<tr>
<td>Melanoma subtypeg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lentigo maligna (HMF)</td>
<td>3 (1)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Insitu melanoma</td>
<td>62 (20)</td>
<td>15 (2)</td>
</tr>
<tr>
<td>Lentigo maligna melanoma</td>
<td>9 (3)</td>
<td>62 (10)</td>
</tr>
<tr>
<td>Superficial spreading melanoma</td>
<td>138 (44)</td>
<td>239 (39)</td>
</tr>
<tr>
<td>Nodular melanoma</td>
<td>27 (9)</td>
<td>50 (8)</td>
</tr>
<tr>
<td>Other melanomas h</td>
<td>4 (0)</td>
<td>35 (6)</td>
</tr>
<tr>
<td>Melanoma not specified</td>
<td>72 (33)</td>
<td>145 (24)</td>
</tr>
<tr>
<td>No previous melanoma f</td>
<td>n/a</td>
<td>51</td>
</tr>
<tr>
<td>Anatomical locationi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lip, eyelid, and facei</td>
<td>10 (3)</td>
<td>63 (11)</td>
</tr>
</tbody>
</table>

179
Scalp and neck 14 (5) 34 (6)
Trunk 138 (44) 206 (37)
Upper limb and shoulder 73 (23) 134 (24)
Lower limb and hip 69 (22) 119 (21)
Not otherwise specified 7 (2) 0
No previous melanoma 5

IQR: Interquartile range, HMF: Hutchinson’s Melanotic freckle

\( ^a \) Data from The 45 and Up Study, linked to the Medicare Benefits Schedule, Admitted Patient Data Collection and Cancer Registry data.
\( ^b \) Groups are not mutually exclusive. Two more characteristic groups were included in the High Risk Clinic a. personal history of melanoma and dysplastic nevus syndrome and b. confirmed CDKN2A gene mutation.
\( ^c \) Family history was confirmed for the High Risk Clinic group and self-reported in the standard care group.
\( ^d \) A personal history of at least two invasive primary melanomas, one melanoma diagnosed in the last ten years.
\( ^e \) Index of Relative Social-Economic Disadvantage is based on the Australian Bureau of Statistics ranking of geographical areas according to relative socio-economic disadvantage from the Socio-Economic Indexes for Areas (SEIFA) 2013. The geographic unit was statistical local area for standard care patients and postal area for high risk clinic patients.
\( ^f \) Not all patients in the standard care group had a previous melanoma recorded prior to 2006. Of these 51 patients, 20 patients reported a family history of melanoma and 31 patients had two or more invasive melanomas between 2006 and 2008.
\( ^g \) Groups based on ICD-10-AM morphology coding for cutaneous melanoma.
\( ^h \) Includes types; acral lentiginous melanoma, balloon cell melanoma, amelanotic melanoma, regressing melanoma, spindle cell melanoma, epithelioid melanoma, mixed epithelioid and spindle cell melanoma, desmoplastic melanoma
\( ^i \) Groups based on ICD-O-3 topography codes for skin sites.
\( ^j \) Includes topography codes: C440, C441, C442, C443.
Table S7.2. Medicare Benefits Scheme item numbers for calculation of health service use

<table>
<thead>
<tr>
<th>Definition</th>
<th>Medicare Benefits Scheme item numbera</th>
</tr>
</thead>
<tbody>
<tr>
<td>General practitioner consultation</td>
<td>3 23 36 44 53 54</td>
</tr>
<tr>
<td>Specialist consultation</td>
<td>00104 00105 00110 00116 00133</td>
</tr>
<tr>
<td>Melanoma excision</td>
<td>31300 31305 31310 31315 31320 31325 31330 31335 31340 31345</td>
</tr>
<tr>
<td>Keratinocytic excision</td>
<td>30196 30197 31255 31256 31257 31258 31260 31261 31262 31263 31265 31266 31270 31271 31273 31275 31276 31277 31278 31280 31281 31282 31283 31284 31285 31286 31287 31288 31290 31291 31292 31293 31295 30202 30203</td>
</tr>
<tr>
<td>Incision or shave biopsy</td>
<td>30071</td>
</tr>
<tr>
<td>Benign lesion excision</td>
<td>30192 30195 31200 31205 31210 31215 31220 31225 31230 31235 31240</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td>134 17603 17610 17615 17620 17640 20100 20300 30400 20420 20700 20730 20820 20900 21100 21110 21195 21199 21300 21600 21610 21700 21800 21460 21199 21460 30055 30075 31432 31435 45200 45203 45206 45207 45400 45403 45439 45442 45445 45448 45451 45563 45665 45668 45669 51300 51303 51306 51309 51312 51315 51318</td>
</tr>
<tr>
<td>Staging procedure</td>
<td>30299 30300 30302 30329 30330 30332 30335 30336 30551 55808 55011 55032 55036 55812 55816 55817 55818 55819 55844 56001 56007 56047 56107 56223 56307 56409 56507 56807 56847 57007 58503 61421 61425 61442 61462 61469 61506 61538 61533 61610 63001 63491 65070 65123</td>
</tr>
<tr>
<td>Treatment</td>
<td>721 31432 31435 66515 13915 13918 13921 13945 15000 15100 15518 15550 15553 15559 15562 15700 15710 13915 13918 13921 31355 73920</td>
</tr>
<tr>
<td>Pathology</td>
<td>72830 72836 72846 72847 72849 72850 72855 72857 73049 73051 73059 73060 73062 73063 73064 73065 73066 73067 73336 73922 73924 73926 73927 73928 73930 73938 73039 73940</td>
</tr>
</tbody>
</table>

*aMedicare item numbers searched to assign a cost for treatment by stage at diagnosis, using the linked data set.*
Table S7.3. Australian Refined Diagnosis-Related Group codes and description of procedures used to estimate hospital costs for patients diagnosed with melanoma on admission to hospital\textsuperscript{a}

<table>
<thead>
<tr>
<th>Code</th>
<th>Description of procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>J08A</td>
<td>Other skin graft and/or debridement procedures with complications or comorbidities</td>
</tr>
<tr>
<td>J08B</td>
<td>Other skin graft and/or debridement procedures without complications or comorbidities</td>
</tr>
<tr>
<td>J10Z</td>
<td>Skin, subcutaneous tissue and breast plastic operating room procedures</td>
</tr>
<tr>
<td>J11Z</td>
<td>Other skin, subcutaneous tissue and breast plastic operating room procedures</td>
</tr>
<tr>
<td>J12A</td>
<td>Lower limb procedures with ulcer/cellulitis with catastrophic complications or comorbidities</td>
</tr>
<tr>
<td>J12B</td>
<td>Lower limb procedures with ulcer/cellulitis without catastrophic complications or comorbidities with skin graft/flap repair</td>
</tr>
<tr>
<td>J12C</td>
<td>Lower limb procedures with ulcer/cellulitis without catastrophic complications or comorbidities without skin graft/flap repair</td>
</tr>
<tr>
<td>J13A</td>
<td>Lower limb procedures with ulcer/cellulitis with catastrophic complications or comorbidities or with (skin graft and severe complications or comorbidities)</td>
</tr>
<tr>
<td>J13B</td>
<td>Lower limb procedures without ulcer/cellulitis without catastrophic complications or comorbidities or without (skin graft and severe complications or comorbidities)</td>
</tr>
<tr>
<td>R02A</td>
<td>Other neoplastic disorders with major operating room procedures with catastrophic complications or comorbidities</td>
</tr>
<tr>
<td>R02B</td>
<td>Other neoplastic disorders with major operating room procedures with severe or moderate complications or comorbidities</td>
</tr>
<tr>
<td>R02C</td>
<td>Other neoplastic disorders with major operating room procedures without complications or comorbidities</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Cost calculated based on length of stay in hospital. Procedure codes searched to assign a cost for hospital treatment by stage at diagnosis, using the linked data set.
Table S7.4. Calculation of hospital admission cost for wide excision and sentinel node biopsy

<table>
<thead>
<tr>
<th>Definition</th>
<th>N</th>
<th>mean cost AUD 2010</th>
<th>mean cost AUD 2013</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>In situ melanoma and hospital admission&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16</td>
<td>2560</td>
<td>2858</td>
<td>2352-3364</td>
</tr>
<tr>
<td>Stage I melanoma and hospital admission&lt;sup&gt;a&lt;/sup&gt;</td>
<td>82</td>
<td>2797</td>
<td>3102</td>
<td>2430-3773</td>
</tr>
<tr>
<td>Stage II melanoma and hospital admission&lt;sup&gt;a&lt;/sup&gt;</td>
<td>44</td>
<td>5071</td>
<td>5661</td>
<td>3584-7738</td>
</tr>
<tr>
<td>Hospital cost for wide excision&lt;sup&gt;b&lt;/sup&gt;</td>
<td>98</td>
<td>2665</td>
<td>2975</td>
<td>2417-3533</td>
</tr>
<tr>
<td>Hospital cost for sentinel lymph node biopsy&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>2686</td>
<td>1167-4205</td>
</tr>
</tbody>
</table>

<sup>a</sup>Cancer Registry confirmed in situ or pseudo-Stage I melanoma preceding a hospital admission with melanoma as the primary reason for admission code in same year.

<sup>b</sup>Mean cost for hospitalisation for in situ and pseudo-Stage I melanoma patients.

<sup>c</sup>Mean cost for hospitalisation of pseudo-Stage II patients minus the hospital cost of a wide excision.
<table>
<thead>
<tr>
<th>Excision type</th>
<th>High Risk Clinic</th>
<th>Standard care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Probability</td>
</tr>
<tr>
<td>Melanoma</td>
<td>16</td>
<td>0.120</td>
</tr>
<tr>
<td>Keratinocytic lesion</td>
<td>24</td>
<td>0.180</td>
</tr>
<tr>
<td>Benign lesion</td>
<td>67</td>
<td>0.504</td>
</tr>
<tr>
<td>Melanoma &amp; keratinocytic lesion</td>
<td>3</td>
<td>0.023</td>
</tr>
<tr>
<td>Melanoma &amp; benign lesion</td>
<td>9</td>
<td>0.068</td>
</tr>
<tr>
<td>Keratinocytic &amp; benign lesion</td>
<td>34</td>
<td>0.090</td>
</tr>
<tr>
<td>Melanoma &amp; keratinocytic &amp; benign lesion</td>
<td>2</td>
<td>0.015</td>
</tr>
<tr>
<td>TOTAL persons with an excision</td>
<td>155</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**

- **a** Base case year was the first year of surveillance.
- **b** Base case year was 2008.
- **c** Relates to first branch from lesion excised on decision tree Figure S3.
- **d** Relates to first branch from lesion excised on decision tree Figure S3.
- **e** Branch included probability of keratinocytic lesion only excision or a melanoma and keratinocytic lesion within the same year.
- **f** Branch included probability of benign lesion only excision or melanoma and benign lesion or a keratinocytic lesion and benign lesion or melanoma and keratinocytic and benign lesion excision within the same year.
- **g** Total persons who had a melanoma, keratinocytic or benign lesion excised. Does not include persons who had only incision or shave biopsies.
<table>
<thead>
<tr>
<th>Distribution</th>
<th>Variable</th>
<th>Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma</td>
<td>Cost of specialised surveillance</td>
<td>887</td>
<td>73</td>
</tr>
<tr>
<td>Gamma</td>
<td>Cost of standard care surveillance</td>
<td>70</td>
<td>36</td>
</tr>
<tr>
<td>Gamma</td>
<td>Cost of hospital wide excision</td>
<td>2,675</td>
<td>2,818</td>
</tr>
<tr>
<td>Gamma</td>
<td>Cost of hospital treatment for Stage III diagnosis</td>
<td>11,492</td>
<td>10,984</td>
</tr>
<tr>
<td>Gamma</td>
<td>Cost of hospital treatment for Stage III metastatic disease</td>
<td>121,732</td>
<td>29,505</td>
</tr>
<tr>
<td>Beta</td>
<td>Probability of an excision in specialised surveillance</td>
<td>0.395</td>
<td>0.074</td>
</tr>
<tr>
<td>Beta</td>
<td>Probability of an excision in standard care</td>
<td>0.640</td>
<td>0.04</td>
</tr>
<tr>
<td>Beta</td>
<td>Probability of an insitu melanoma in specialised surveillance</td>
<td>0.45</td>
<td>0.132</td>
</tr>
<tr>
<td>Beta</td>
<td>Probability of a Stage I melanoma in specialised surveillance</td>
<td>0.42</td>
<td>0.107</td>
</tr>
<tr>
<td>Beta</td>
<td>Probability of a Stage II melanoma in specialised surveillance</td>
<td>0.096</td>
<td>0.085</td>
</tr>
<tr>
<td>Beta</td>
<td>Probability of a Stage III melanoma in specialised surveillance</td>
<td>0.027</td>
<td>0.045</td>
</tr>
<tr>
<td>Beta</td>
<td>Probability of a Stage IV melanoma in standard care</td>
<td>0.149</td>
<td>0.04</td>
</tr>
<tr>
<td>Beta</td>
<td>Probability of a Stage I melanoma in standard care</td>
<td>0.585</td>
<td>0.057</td>
</tr>
<tr>
<td>Beta</td>
<td>Probability of a Stage II melanoma in standard care</td>
<td>0.216</td>
<td>0.054</td>
</tr>
<tr>
<td>Beta</td>
<td>Probability of a Stage III melanoma in standard care</td>
<td>0.045</td>
<td>0.012</td>
</tr>
<tr>
<td>Beta</td>
<td>Utility insitu diagnosis</td>
<td>0.687</td>
<td>0.192</td>
</tr>
<tr>
<td>Beta</td>
<td>Utility Stage I diagnosis</td>
<td>0.579</td>
<td>0.272</td>
</tr>
<tr>
<td>Beta</td>
<td>Utility Stage II diagnosis</td>
<td>0.579</td>
<td>0.272</td>
</tr>
<tr>
<td>Beta</td>
<td>Utility Stage III diagnosis</td>
<td>0.535</td>
<td>0.278</td>
</tr>
<tr>
<td>Beta</td>
<td>Utility Stage IV diagnosis</td>
<td>0.583</td>
<td>0.192</td>
</tr>
<tr>
<td>Beta</td>
<td>Utility insitu surveillance</td>
<td>0.809</td>
<td>0.179</td>
</tr>
<tr>
<td>Beta</td>
<td>Utility Stage I surveillance</td>
<td>0.820</td>
<td>0.165</td>
</tr>
<tr>
<td>Beta</td>
<td>Utility Stage II surveillance</td>
<td>0.802</td>
<td>0.165</td>
</tr>
<tr>
<td>Beta</td>
<td>Utility Stage III surveillance</td>
<td>0.703</td>
<td>0.156</td>
</tr>
<tr>
<td>Beta</td>
<td>Utility Stage IV surveillance</td>
<td>0.796</td>
<td>0.167</td>
</tr>
<tr>
<td>Beta</td>
<td>Utility benign excision</td>
<td>0.971</td>
<td>0.047</td>
</tr>
<tr>
<td>Beta</td>
<td>Utility keratinocytic lesion excision</td>
<td>0.976</td>
<td>0.052</td>
</tr>
</tbody>
</table>
NSW: New South Wales

**Figure S7.1.** Data linkage diagram for identification of the standard care high risk cohort. Study participants from the Sax Institute’s 45 and Up study were linked, facilitated by the Centre for Health Record Linkage, with records from the NSW Cancer Registry hospitalisation data from the Admitted Patient Data Collection. These records were held by the Sax Institute in a secure research database through which a high risk cohort of 45 and Up study participants could be identified (“standard care group”) and health service usage calculated.
Figure S7.2. A Markov model showing the transition between health states from patient presenting for surveillance. All patients begin with a suspicious lesion presenting for surveillance. If a lesion is identified, a suspicious lesion may be a melanoma and/or keratinocytic lesion and/or benign lesion. Dependant on the type of lesion excised, the patient may return to present for surveillance or move to another health state. If the lesion is a melanoma, the health state is determined by stage at diagnosis. All health states have an associated cost and utility score associated with treatment. The model has six health states; 1) Patient presents for surveillance, 2) Dead from other causes, 3) Dead due to melanoma and three health states related to progression of disease (not shown) 4) Recurrence of melanoma, 5) Stage III disease 6) Stage IV disease.
Figure S7.3. Decision tree structure showing potential pathways dependent on the type of lesion identified for treatment within one year. For example, a patient may have two types of lesion identified for treatment and may have more than two excisions within the year. For standard care, the model assumes all lesions identified for excision occur during the one skin surveillance appointment. In the high risk clinic, all patients are seen twice a year. Based on our empirical data, the model uses constant probabilities for the number and type of suspicious lesions treated over the study period. See Table S7.5 for model inputs.
**Figure S7.4.** Matrix for calculation of the mean annual cost for Stage III. The mean annual cost for Stage III included the mean cost of hospital admission for sentinel lymph node dissection and a patient’s continuing specialist treatment up to 12 months from the date of hospital admission. Continuing treatment costs were calculated from the date of discharge using selected Medicare Benefits Schedule item numbers for treatment, staging and pathology (Table 3 Supplementary materials). Costs for item numbers were included for specialty group combinations shown as linked.

<table>
<thead>
<tr>
<th>Provider speciality</th>
<th>Specialty group</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Surgical</td>
<td>Consultation</td>
</tr>
<tr>
<td>Dermatology</td>
<td>Diagnostic imaging</td>
</tr>
<tr>
<td>Plastic surgery</td>
<td>Pathology services</td>
</tr>
<tr>
<td>Anatomical pathology</td>
<td></td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
</tr>
<tr>
<td>Radiation oncology</td>
<td></td>
</tr>
<tr>
<td>Pathology non-specialist</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specialty group</th>
<th>Provider speciality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultation</td>
<td>General Surgical</td>
</tr>
<tr>
<td>Diagnostic imaging</td>
<td>Dermatology</td>
</tr>
<tr>
<td>Pathology services</td>
<td>Plastic surgery</td>
</tr>
<tr>
<td></td>
<td>Anatomical pathology</td>
</tr>
<tr>
<td></td>
<td>Pathology</td>
</tr>
<tr>
<td></td>
<td>Radiation oncology</td>
</tr>
<tr>
<td></td>
<td>Pathology non-specialist</td>
</tr>
</tbody>
</table>
Figure S7.5. Results of one-way sensitivity analysis for High Risk Clinic vs standard care. The graph shows that the probability of excision in standard care was the only variable that may change the model result and increase the incremental cost-effectiveness ratio above $50,000 per quality adjusted life year gained. All variables were tested in one-way sensitivity analysis, and variables with the greatest effect on the model results retained.
8 Discussion and conclusion

8.1 Main findings

This thesis presented an overview of guideline recommendations and management of individuals at high-risk of melanoma in New South Wales, Australia. The review of practice guidelines applicable to the identification and management of individuals at high-risk of cutaneous melanoma\(^1\) found that recommendations relating to identification, surveillance and follow-up strategies were inconsistent and varied between countries. This was largely due to low levels of evidence but also variation in the classification of risk groups. The analysis of clinician’s management of individual’s high risk of melanoma in New South Wales found that melanomas were more frequently detected by doctors in general practice compared to specialists, and doctors were by-and-large following clinical practice guidelines by recommending ongoing surveillance. While the majority of dermatologists and primary care doctors in skin cancer clinics were using dermoscopy to examine suspicious lesions, primary care doctors in other general practice settings had lower (98% vs 43% respectively) rates of use. We also found that melanomas detected by doctors were thinner than melanomas detected by patients. The analysis of characteristics of high-risk patients found that they present at a younger age than average risk patients and were more likely to have their melanomas on areas with intermittent (limbs) or limited sun exposure (i.e. limbs or trunk), body sites which are usually covered by clothing and thus may be harder to detect oneself. It is therefore important that high-risk patients be identified and have their risk factors assessed, to ensure appropriate surveillance. The micro-costing study of a specialised High Risk Clinic\(^2\) presented in chapter 5 found that while surveillance requires trained staff and specialised
equipment, the mean cost of surveillance from both a health system and societal perspective were very similar as patients were willing to give up a lot of their own work or leisure time to attend follow-up appointments.

The main finding from this thesis, and representing the largest body of work, was that surveillance of individuals at high risk of melanoma in a specialised High Risk Clinic was a cost-effective strategy compared with standard care. The High Risk Clinic was less expensive and more effective compared to standard care, primarily because melanomas were detected at an earlier stage and there were fewer excisions performed during skin surveillance by High Risk Clinic staff, directly impacting upon treatment and pathology service costs. In the High Risk clinic, a ‘wait and watch’ approach was usually adopted, whereas in the community a suspicious lesion appeared more likely to be excised. The reasons for a doctor deciding to excise a suspicious lesion are many, and are influenced by patient characteristics, time demands on patients and doctors, and other external factors such as travel distance or fee for service structure.3-5

8.2 Limitations and strengths

Ideally, the cost-effectiveness of surveillance through the High Risk Clinic compared to standard care would be best assessed using a randomised controlled trial study design. The High Risk Clinic study was not designed with a control arm and therefore for the comparator group we used a linked population-based dataset, which is the best available data for our purpose. We matched the characteristics of the standard care group as closely as possible to the High Risk Clinic group, however this could not be done perfectly, which led to some
differences between groups in characteristics such as age, sex, socio-economic status, dysplastic nevus syndrome and confirmation of family history. For example, the definition of family history was based on self-reported number of first-degree relatives with melanoma and for the linked dataset, but was based on confirmed melanoma (using medical records) in first or second-degree relatives for High Risk Clinic participants. While there was a similar percentage of participants with a family history in both standard care and High Risk Clinic arms (15% vs 16%, respectively), the level of risk associated with this risk factor may be stronger in the High Risk Clinic because the histories were confirmed and more extensive. This might have led to more melanomas in the High Risk Clinic arm and under-estimation of the cost-effectiveness. On the other hand, the standard care group had a higher proportion of men, was slightly older on average and with higher socio-economic disadvantage than those attending the High Risk Clinic. Lower educational attainment, male gender and older age have been linked to presentation with a more advanced stage of melanoma in Australia, and risk of melanoma and keratinocytic cancer increases with age. These demographic characteristics may have accentuated differences in stage of disease at presentation and increased excision rates and thus potentially led to overestimation of the cost of surveillance in the standard care arm of the model. We did examine these variables closely in one-way, two-way and probabilistic sensitivity analyses and found that within their plausible ranges, the overall results were not changed, indicating that the conclusion of the model was reliable. In addition, in the Monte Carlo simulation used to evaluate the incremental cost and incremental effectiveness between the two strategies, the 95%CI of the ICERs fell predominantly in the south-east quadrant of the cost-effectiveness plane, indicating in most modelled scenarios that High Risk Clinic was more effective and less expensive than standard care.
We were very fortunate to obtain access to cancer registry reports of subsequent melanomas and in situ melanomas, as these data are usually not published by the cancer registry. However, they do not contain the same level of information in the cancer registry as original invasive melanoma reports. As a result, for invasive melanomas a simplified classification of stage of diagnosis had to be created based on stage at diagnosis and lesion depth. Sensitivity analysis showed no effect on the overall results when we increased the percentage of in situ melanomas in standard care as there was still a higher percentage of patients with third and fourth stage disease in standard care.

It was not possible to directly measure preference-based quality of life scores (utilities) from High Risk Clinic and standard care participants. Instead, I conducted a literature review to guide the selection of utility measures. We ultimately chose measurements from a study in Belgium, a country with similar treatment and surgical management to Australia, which calculated utilities at diagnosis and also following treatment when the authors considered the patients were considered in remission.\(^8\) The utility scores were also validated against population health-assessment based (EQ-5D-5L)\(^9\) and health-specific based (Fact-M)\(^10\) measures to ensure an accurate estimation of the quality of life effects of the disease process, which is important in melanoma as morbidity is related to stage at diagnosis.\(^11\)

Some High Risk Clinic costs for the cost-effectiveness analysis were obtained from our micro-costing study.\(^2\) These estimations were derived from observing resource use in a hospital-based dermatology outpatient clinic. Costs for clinics in other settings may vary due to the choice of technology or location. An important contributor to the High Risk Clinic costs were labour costs due to the number of patient visits and administration required. The
A sensitivity analysis of the cost-effectiveness study showed that based on current excision rates and all else being equal, even if costs doubled, the High Risk Clinic model would remain cost-effective.

A strength of the study was the detailed and comprehensive data available for the High Risk Clinic and standard care groups. The linked population dataset enabled the identification of a cohort of high-risk individuals from the community, and included 45 and Up cohort study questionnaire responses, cancer registry data for all invasive and in situ melanoma reports, Medicare claims data and hospital inpatient data. The linked population dataset contained real-world data on skin cancer treatment, excision numbers and hospital costs, overcoming limitations of studies that are based on self-report or non-representative samples. We were also able to calculate a plausible range around standard care estimates to use in the sensitivity analyses. In addition, other information about the management of high-risk individuals was able to be obtained from the population-based Melanoma Patterns of Care study data. A calculation of a cost per QALY ensures that the study is comparable with other health care interventions.

The main limitation of studies examining the characteristics and management of high-risk patients in NSW was that we were unable to obtain more detailed information about risk factors, for example the number of naevi, the number of affected relatives, and number of previous melanomas.
8.3 Other studies

Most studies that have examined surveillance costs for melanoma patients have focused on recurrence (regional and distant spread) of melanoma, and have provided risk-adapted follow-up strategies based on stage at diagnosis. \textsuperscript{12-15} Studies that focused on melanoma patients with early-stage (in situ or stage I) melanoma \textsuperscript{16-18} reported physical examination compared to other most commonly used screening modalities the most cost-effective strategy, but did not provide information on how surveillance might be conducted. Some studies calculated costs and inferred savings based on the likelihood of and costs of detecting metastases in patient’s diagnosed with Stage I or II. \textsuperscript{12,18} One study \textsuperscript{19} calculated the costs and quality-adjusted-life-years (QALYs) for surveillance of Stage I patients from a societal perspective using a strategy of decreased follow-up intervals and ceasing surveillance after ten years; this strategy delivered savings of $174,000/QALY (1996 US dollars). \textsuperscript{19} It is worth noting that these savings were based on patients not developing metastasis and reducing chest X-rays. In their study, 80% of the surveillance costs were due to chest X-rays, which are no longer recommended for Stage I patients in Australia. \textsuperscript{20} While several studies have reported on the diagnostic benefits of monitoring high-risk patients, \textsuperscript{21-25} none included estimations of the costs of these surveillance measures. A recent study examining patients with a small number of dysplastic naevi, did find the use sequential digital dermoscopy cost effective because number of benign atypical lesions excised were reduced. \textsuperscript{26}

Most cost-effectiveness studies involving melanoma patients relate to newer therapies such as BRAF inhibitors \textsuperscript{27-29} or other strategies for treating metastatic disease. \textsuperscript{30} However, some studies have been conducted on the cost-effectiveness of conducting population-based skin...
examination.\textsuperscript{31-34} One American study found that population screening would be cost-effective if high-risk patients were screened.\textsuperscript{34} Another US study\textsuperscript{31} reporting on the use of a range of screening strategies for adults over 50 years with different relative risk (RR) for melanoma, compared screening with a ‘do-nothing’ approach and found that one total body examination would be cost-effective, with an incremental cost-effectiveness ratio (ICER) of $10,100/QALY (2007 US dollars). In siblings of a patient with melanoma (RR 2.54) the ICER was $4000/QALY gained. For individuals with two affected first-degree relatives (RR 5.56) the ICER was $900/QALY gained for one examination, $14 700/QALY gained for surveillance every two years and $99,800/QALY gained for annual screening. Another study compared the dermatologists’ time to conduct total body examination versus lesion-directed screening.\textsuperscript{33} While both methods had a similar skin cancer detection rate, a total body examination took 6 times longer than lesion-directed screening; mean time 171.6 (SD 62.7) seconds versus 24.2 (SD 31.8) seconds excluding the time patients took to dress and undress. However, patients had significantly higher anxiety scores following lesion-directed screening. In that study, the majority of patients would not be considered at high-risk for melanoma, as less than 14% of patients had more than 50 naevi and less than 10% reported any family history. The study concluded that if a patient presented with a suspicious lesion then total body examination should be conducted.\textsuperscript{33}

8.4 Implications for policy and practice

A previous analysis of outcomes from participants in the High Risk Clinic showed that monitoring patients assisted with the early diagnosis of melanoma.\textsuperscript{35} This High Risk Clinic model of care has the potential to change clinical practice because the evidence from our
cost-effectiveness analysis shows that fewer excisions for suspicious lesions take place in the High Risk Clinic. Additionally there is less morbidity (and thus probably mortality) as melanomas are detected at an earlier stage in the High Risk Clinic than in standard care in the community. A review of the cost-effectiveness of long-term follow-up programs for cancer survivors (all cancers, not just melanoma), stated that a less intensive follow-up program utilising primary care providers was generally shown to be the most cost-effective approach.\textsuperscript{36} Factors contributing to surveillance costs were frequency of follow-up visits, length of surveillance programs, patient age, stage of disease and years following diagnosis. Programs that were more cost-effective, included strategies for risk-adapted follow-up according to age and other options for service delivery.\textsuperscript{36} The findings from our study indicate that rather than contributing to over-treatment, the careful ‘watch and wait’ approach to suspicious skin lesions in the High Risk Clinic resulted in fewer excisions and lower costs compared to surveillance in the community.

Wider implementation of the High Risk Clinic surveillance protocol on a state-wide or national basis would require estimation of the number of people who would be eligible for the service, and strategies to ensure only eligible patients accessed the service and that a high-quality service was provided. This specialised surveillance could be performed by dermatologists as well as primary care physicians with additional training and accreditation. Further research into the impact on the government healthcare budgets and societal costs would provide additional information about the projected uptake and service provision. The use of Medicare Benefits Schedule item numbers for total body photography or sequential dermoscopy has the potential to decrease patient out-of-pocket costs for surveillance and distribute the cost between state and federal health systems.
8.5 Directions for future research

The diagnosis, management and pathology service use related to skin cancer is a costly public health problem.\textsuperscript{37} Discussion regarding potential over-diagnosis due to increased surveillance is important.\textsuperscript{38,39} Melanoma patients require ongoing surveillance and a full skin examination is a critical component of follow-up following a melanoma diagnosis. The detection of subsequent melanomas and keratinocytic lesions following melanoma diagnosis and potential over-diagnosis may be due in part to closer monitoring and heightened awareness of both patients and their doctors following diagnosis.\textsuperscript{40} There are many reasons that a doctor may decide to treat and excise the lesion rather than take a ‘watch and wait approach’. Reasons include clinical experience, the desire not to misdiagnose, patient pressure, time and work constraints for both the clinician and patient, and/or a fee-for-service payment structure which reimburses doctors for individual items of service, which might incentivise some doctors to excise rather than prescribe a topical cream.\textsuperscript{3,5,41,42} These factors warrant further investigation, as there may be avenues for potential improvements in current practice in the community setting.

The extension of the High Risk Clinic model of care to three more centres (as mentioned in the Introduction chapter 1) will provide evidence to validate the surveillance protocol benefits and costs in other clinical settings, including a skin cancer clinic and private dermatology practice. Other research should also be conducted on whether the eligibility criteria should be expanded to melanoma patients at moderate-risk of a new primary melanoma, not just those at very high-risk, or to other groups at high risk of skin cancer such as organ transplant or immunosuppressed patients. Further information that would support implementation of the
High Risk Clinics include finding out how many patients in NSW will be eligible to attend, how patients will find out about High Risk Clinics, where they should be located for example in a high volume hospital centre and whether the protocol should be kept the same or adapted for different levels of risk.

The current study was limited to the health service perspective. Assessment of societal costs would provide a broader perspective including assessment of patient costs e.g. patient out-of-pocket costs for travel, specialists or treatment and costs to society in terms of productivity losses and potential life years lost for death. The potential costs to patients and impact on access to surveillance services should also be assessed. Factors that will impact out-of-pocket costs include location of clinics, accessibility of the clinics, the frequency of the clinic visits and the costs of associated services such as total body photography and, when required, digital monitoring, excisions and support services. Although there was high level of compliance to attending for surveillance, the reasons why some patients drop out could also be examined.

At the High Risk Clinic, patients were instructed in skin self-examination when their total body photographs were taken. The value of the education component of instructing these patients in skin self-examination, exploring which technique is most beneficial or the psychosocial benefits of this education have not been fully investigated. Despite low levels of evidence for the benefits of self skin-examination, this recommendation is in most clinical practice guidelines because of the importance of early detection. It has been reported that younger people are more likely to detect their own melanoma. However, full body skin examination remains important after diagnosis of melanoma, as the risk of developing another melanoma is 5-9 times more likely than the general population.
8.6 Conclusion

The studies presented in this thesis have strong potential to influence clinical practice and public policy regarding the management of individuals at high-risk of developing melanoma. Our cost-effectiveness study showed, from a health service perspective, that specialised surveillance of high-risk people in a High Risk Clinic may be more efficient than standard care in the community. Implementation of this service would provide an opportunity for currently used resources to be redirected within the health care system. Further research is required to assess the wider budget implications and assist with implementation of this specialised service.
8.7 References


A Belgian Study of Patients with a Single or a Small Number of Atypical Nevi. *PloS one.* 10/1403/31/received 09/04/accepted 2014;9(10):e109339.


## Appendices

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.1</td>
<td>Questionnaires from Melanoma Patterns of Care study</td>
<td>207</td>
</tr>
<tr>
<td>9.2</td>
<td>National Ethics Application Form application and Protocol</td>
<td>216</td>
</tr>
<tr>
<td>9.3</td>
<td>Ethics approvals</td>
<td>261</td>
</tr>
<tr>
<td>9.4</td>
<td>Review of published health utilities for excisions</td>
<td>274</td>
</tr>
<tr>
<td>9.5</td>
<td>Survey of clinical pathway in standard care</td>
<td>282</td>
</tr>
</tbody>
</table>
**Melanoma Patterns of Care Study**  
**Primary treatment questionnaire 1**

1. In what practice setting did you see this patient?  
- General Practice  
- Skin cancer clinic  
- Other  Please specify: ____________________

2. Date of first presentation to you with this melanoma?  
   ___ / ___ / ___

3. Did the patient have a personal history of melanoma?  
- No  
- Yes  
- Don’t know

4. Did the patient have a family history of melanoma in a blood relative?  
- No  
- Yes  
- Don’t know

5. Did this patient have lots of moles?  
- No  
- Yes  
- Don’t know

6. How did this melanoma present? (Tick one only)  
- Patient reported this skin lesion  
- Found incidentally when checking another skin lesion  
- Found in a routine skin check  
- Other  Please specify: ____________________

7. Was there a history of: (Tick all that apply)  
- Change in colour, size, elevation or shape of lesion?  
- Bleeding?  
- Itch?  
- Ulceration?

8. What was the lesion’s site? (Tick one only)  
- Head or neck  
- Anterior trunk  
- Posterior trunk  
- Upper limb  
- Lower limb

9. Did you observe this lesion for a period before biopsy?  
- No  
- Yes  If yes, how long? ____________________

10. Was the lesion clinically a melanoma?  
- No  
- Suspicious  
- Yes

11. Any clinically suspicious lymph nodes?  
- No  
- Yes  If yes, please specify location(s).

12. Any clinical signs of distant spread (other than suspicious lymph nodes)?  
- No  
- Yes  If yes, please specify location(s).

13. What investigations did you do? (Tick all that apply)  
- None  If none, jump to Q15.  
- Chest x-ray  
- Biochemistry or haematology  
- CT scan  
- MRI scan  
- PET scan  
- Bone scan  
- Other  Please specify: ____________________

14. Was there any investigational evidence of metastatic spread?  
- No  
- Yes  If yes, please specify location(s).

15. Did you assess the lesion with a dermoscope?  
- No  
- Yes  
- Don’t know

16. Did you refer the patient to another doctor before biopsy?  
- No  
- Yes  If yes, jump to Q22.

17. Did you attempt a complete excision biopsy?  
- No  
- Yes  
- If yes, was it complete?  
  - No  
  - Yes  Please continue to next page.
If yes, please specify.
Excision margin ____ mm
Did you remove subcutaneous tissue with this lesion?  
☐ No  
☐ Yes  Jump to Q19.

18. Did you do a partial biopsy?  
☐ No  
☐ Yes  If yes, please specify type.  
☐ Punch biopsy  
☐ Shave biopsy  
☐ Partial incision biopsy

If yes, did you think it was a non-melanocytic lesion?  
☐ No  
☐ Yes

Your post-biopsy treatment of the primary melanoma

19. How did you manage the primary lesion next?  
☐ Wide excision  
  Please specify:  
  Date of wide excision ____ / ____ / ____  
  Time from biopsy to wide excision ____ days  
  Excision margin ____ mm  
☐ Observation only  Jump to Q22.  
☐ Referral to a specialist  Jump to Q22.

If you did a wide excision:  
20. How was surgical repair done?  
☐ Primary closure  
☐ Flap  
☐ Skin graft

21. Were there any post-op complications?  
☐ No  
☐ Wound infection  
☐ Wound breakdown  
☐ Lymphoedema  
☐ Prolonged pain  
☐ Seroma or haematoma  
☐ Other  Please specify. ________________  
☐ Don’t know

Follow-up

22. Did you recommend follow-up?  
☐ No  
☐ Yes  
  Who did you recommend do the follow-up?  
  ☐ Yourself  
  ☐ GP  
  ☐ Dermatologist  
  ☐ Surgeon  
  ☐ Other  Please specify. ________________

How frequently will follow-up be done initially?  
At intervals of ____ months

23. Did you do any of the following?  
Advise patient on specific changes that suggest melanoma?  
☐ Yes  
☐ No  
Encourage patient to perform skin self-examination?  
☐ Yes  If yes, how often? ________________  
☐ No  
Recommend a skin surveillance program?  
☐ Yes  
☐ No

Referrals  
Please give us the names and addresses of any other doctors to whom you referred this patient for melanoma management.

Surgeon  
__________________________________________

Dermatologist  
__________________________________________

Medical oncologist  
__________________________________________

Radiation oncologist  
__________________________________________

Other doctor  Please state specialty if applicable.  
__________________________________________

Who is this patient’s usual family doctor?  
If you are, tick this box  ☐  
Or give name and contact details  
__________________________________________

This is the end of the questionnaire.  
Thank you for your help.
1. In what practice setting did you see this patient?
   - Skin cancer clinic
   - Dermatology
   - Surgery
   - Plastic surgery
   - Other Please specify.

2. Date of first presentation to you with this melanoma? __ / __ / __

Patient’s presentation with this melanoma

Did the patient have a:
3. Personal history of melanoma?
   - No
   - Yes
   - Don’t know

4. Family history of melanoma in a blood relative?
   - No
   - Yes
   - Don’t know

Melanoma risk

5. Did this patient have lots of moles?
   - No
   - Yes
   - Don’t know

Details of primary melanoma

6. How did this melanoma present?
   (Tick one only)
   - Patient reported this skin lesion
   - Found incidentally when checking another skin lesion
   - Found in a routine skin check
   - Other Please specify. ____________________
   - Don’t know

7. Was there a history of: (Tick all that apply)
   - Change in colour, size, elevation or shape of lesion?
   - Bleeding?
   - Itch?
   - Ulceration?

8. What was the lesion’s site? (Tick one only)
   - Head or neck
   - Anterior trunk
   - Posterior trunk
   - Upper limb
   - Lower limb

9. Did you observe this lesion for a period before biopsy?
   - No
   - Yes If yes, how long? ____________________

10. Was the lesion clinically a melanoma?
    - No
    - Suspicious
    - Yes

Metastases

Were there:
11. Any clinically suspicious lymph nodes?
    - No
    - Yes If yes, please specify location(s).
    - Don’t know

12. Any clinical signs of distant spread (other than suspicious lymph nodes)?
    - No
    - Yes If yes, please specify location(s).
    - Don’t know

Investigations

13. What investigations did you do?
    (Tick all that apply)
    - None If none, jump to Q15.
    - Chest x-ray
    - Biochemistry or haematology
    - CT scan
    - MRI scan
    - PET scan
    - Bone scan
    - Other Please specify. ____________________

14. Was there any investigational evidence of metastatic spread?
    - No
    - Yes If yes, please specify location(s).

15. Did you assess the lesion with a dermoscope?
    - No
    - Don’t know
    - Yes

Biopsy of melanoma

16. Did you refer the patient to another doctor before biopsy?
    - No
    - Yes If yes, jump to Q26.

Please continue to next page.
17. Did you attempt a complete excision biopsy?
   - No
   - Yes If yes, was it complete?
     - No
     - Yes If yes, please specify.

   Excision margin _____ mm
   Did you remove subcutaneous tissue with this lesion?
   - No
   - Yes Jump to Q19.

18. Did you do a partial biopsy?
   - No
   - Yes If yes, please specify type.
     - Punch biopsy
     - Shave biopsy
     - Partial incision biopsy

   If yes, did you think it was a non-melanocytic lesion?
   - No
   - Yes

Your post-biopsy treatment of the primary melanoma

19. Did you do a wide excision or wide re-excision?
   - Yes If yes, please specify.
     Date of excision ___ / ___ / ___
     Time from biopsy to excision _____ days
     Excision margin _____ mm
   - No If no, jump to Q22.

   If you did a wide excision or wide re-excision:

20. How was surgical repair done?
   - Primary closure
   - Flap
   - Skin graft

21. Were there any post-op complications?
   - No
   - Wound infection
   - Wound breakdown
   - Lymphoedema
   - Prolonged pain
   - Seroma or haematoma
   - Other Please specify. ____________________
   - Don’t know

Your management of lymph nodes

22. Did you do any of these? (Tick all that apply)
   - Needle aspiration of a lymph node
   - Lymphatic mapping (Tick all that apply)
     - Gamma radiation mapping
     - Vital blue dye mapping
     - Mapping done as part of a clinical trial
   - Sentinel lymph node biopsy
     Number of sentinel nodes removed ______
   - Other staging procedures Please specify. _______________________

23. What lymph node pathology was done? (Tick all that apply)
   - None
   - H & E
   - Immunohistochemistry
   - RT-PCR
   - Other Please specify. _______________________

24. Did you do a complete dissection of regional lymph nodes?
   - No
   - Yes Any post-operative complications?
     - No
     - Wound infection
     - Wound breakdown
     - Lymphoedema
     - Prolonged pain
     - Seroma or haematoma
     - Other Please specify. _______________________

     - Don’t know

     Were margins clear?
     - Yes
     - No

     Intention of complete node dissection? (Tick all that apply)
     - Curative intent
     - Palliative intent

Other treatment

25. Did you give any other specific treatment for this melanoma?
   - No
   - Yes If yes, please specify. _______________________

Please continue to next page.
Stage at diagnosis

26. What was this patient’s “new” AJCC stage of melanoma at diagnosis?  
(Tick the most accurate stage you can)
- 0
- I  □ IIA □ IIB □ IIC
- II □ IIIA □ IIIB □ IIIC
- III □ IIIA □ IIIB □ IIIC
- IV
- Don’t know

Follow-up

27. Did you recommend follow-up?  
- No
- Yes
   Who did you recommend do the follow-up?
   - Yourself
   - GP
   - Dermatologist
   - Surgeon
   - Other  Please specify. ____________

   How frequently will follow-up be done initially?  
   At intervals of ____ months

28. Did you do any of the following?  
Advise patient on specific changes that suggest melanoma?  
- Yes
- No

Encourage patient to perform skin self-examination?  
- Yes  If yes, how often? ______________
- No

Recommend a skin surveillance program?
- Yes
- No

29. Has the patient's melanoma recurred or progressed since they were first treated for this or a synchronous melanoma?  
- No
- Yes  If yes, please specify.
   Date of relapse/progression ___ / __ / ___

Sites  (Tick all that apply)
- Local recurrence
- Regional lymph nodes
- Distant Metastasis

Evidence of recurrence or progression  
(Tick all that apply)
- Clinical assessment
- Histopathology
- Radiology (CT or MRI scan)
- Ultrasound
- Nuclear medicine (PET, bone, liver scan)

30. Did you refer the patient for psychological care?  
- Not applicable
- No
- Referred for psychological care  
   If referred for psychological care, who provided the care?  Please specify discipline.
   __________________________________________

Referrals

Please give us the names and addresses of any other doctors to whom you referred this patient for melanoma management.

Surgeon

_________________________________________

Dermatologist

_________________________________________

Medical oncologist

_________________________________________

Radiation oncologist

_________________________________________

Other doctor  Please state specialty if applicable.

________________________________________

Who is this patient’s usual family doctor?  
If you are, tick this box  □

Or give name and contact details

________________________________________

This is the end of the questionnaire.  
Thank you for your help.
1. What is your type of practice?
- Dermatology
- Surgery
- Plastic surgery
- Medical oncology
- Radiation oncology
- Other
- Please specify.

Patient's presentation to you

2. Date of this presentation to you with this melanoma? __ / __ / __

3. Context of this presentation to you?
- Initial treatment or part of initial treatment
- Treatment of disease which became evident after initial treatment
  If so:
  Date disease again became evident ____ / ____ / ____
  Both

4. Site of primary lesion?
- Head or neck
- Anterior trunk
- Posterior trunk
- Upper limb
- Lower limb
- Don't know

Clinical extent of disease at presentation to you

5. Local or in transit recurrence?
- Yes
- No

6. Involved lymph nodes? (Tick all that apply)
- None involved
- Regional
- Distant
  Please specify location.
  ________________
- Unknown

7. Distant metastases? (Tick all that apply)
- None
- Cutaneous
- Bone
- Lung
- Liver
- Brain
- Other
  Please specify.
  ______________________
- Unknown

Investigations you requested

8. Investigations requested? (Tick all that apply)
- None
- Chest x-ray
- Biochemistry/Haematology
- CT scan
- MRI scan
- PET scan
- Bone scan
- Biopsy of metastatic lesion
- Ultrasound
- Other
  Please specify.

Please complete the following sections when they apply to your management of this patient following this presentation

Surgery

9. Did you do a wide excision or wide re-excision?
- Yes
  If yes, please specify:
  Date of excision ____ / ____ / ____
  Time from biopsy to excision ____ days
  Excision margin ____ mm
- No
  If no, jump to Q12.

If you did a wide excision or wide re-excision:

10. How was surgical repair done?
- Primary closure
- Flap
- Skin graft

11. Were there any post-op complications?
- No
- Wound infection
- Wound breakdown
- Lymphoedema
- Prolonged pain
- Seroma or haematoma
- Other
  Please specify: ______________________
- Don't know

Your management of lymph nodes

12. Did you do any of these? (Tick all that apply)
- Needle aspiration of a lymph node
- Lymphatic mapping (Tick all that apply)
  - Gamma radiation mapping
  - Vital blue dye mapping
  - Mapping done as part of a clinical trial

Please continue to next page.
13. What lymph node pathology was done?  
*(Tick all that apply)*
- None
- H & E
- Immunohistochemistry
- RT-PCR
- Other  *Please specify.*

14. Did you do a complete dissection of regional lymph nodes?  
- Not applicable
- No
- Yes
   - Any post-operative complications?  
     - No
     - Wound infection
     - Wound breakdown
     - Lymphoedema
     - Prolonged pain
     - Seroma or haematoma
     - Other  *Please specify.*
   - Don’t know
   - Were margins clear?  
     - Yes
     - No
   - Intention of complete node dissection?  
     *(Tick all that apply)*  
     - Curative intent
     - Palliative intent

15. Did you resect any melanoma metastases?  
- Not applicable
- No
- Yes  
  *Please specify site(s) of metastases resected.*

16. Did you give, are you giving, or do you intend to give the patient chemotherapy?  
- No
  - Offered but declined
  - Not indicated
  - Other reason  *Please specify.*

17. Did you give or refer the patient for regional therapy, i.e. perfusion or infusion with cytotoxic agents?  
- No
  - Not applicable
  - Gave therapy  *Please specify type.*
  - Referred for therapy  *Please specify type.*
Radiotherapy

18. Did you give or are you giving the patient radiotherapy?
   - No
     - Not applicable
     - Offered but patient declined
   - Yes
     - Intention of radiotherapy (Tick all that apply)
       - Curative intent
       - Palliative intent
       - Adjuvant treatment (e.g. after axillary dissection)

   Site irradiated
   - Axilla
   - Bone
   - Groin
   - Whole brain
   - Other  Please specify. __________________________

   Dose per fraction: ____ Grays
   Total dose:
   ____ (Grays) in ____ fractions
   ____ days OR ____ weeks

Immunotherapy

19. Did the patient receive immunotherapy?
   - No
     - Offered but declined
     - Not indicated
     - Other reason
   - Yes  If yes, please provide details.
     (Tick all that apply)
     - Interferon alpha-2b
     - IL-2
     - Vaccine  Please specify. __________________________
     - Other  Please specify. __________________________

   Planned immunotherapy duration: _____ months
   Treatment start date: ___ / ___ / ___

   Has treatment finished?
   - Yes  Finish date: ___ / ___ / ___
   - No

   Dosage: ___________  Units: ___________

   Toxicity
   - Significant
   - Moderate
   - Minor

Please complete all sections from here on.

Other management

20. Did you give or refer the patient for any systemic therapy not mentioned above?
   - Not applicable
   - No
   - Gave systemic therapy  Please specify type.

   Referred for systemic therapy  Please specify type.

21. Is this patient on a clinical trial?
   - No
   - Yes  If yes, please specify.

22. Did you refer the patient for psychological care?
   - Not applicable
   - No
   - Referred for psychological care
     If referred for psychological care, who provided the care? Please specify discipline.

23. Was this patient referred to specialised palliative care?
   - Not applicable
   - No
   - Yes
   - Don’t know

24. Was this patient’s care discussed in a multidisciplinary team meeting?
   - No
   - Patient was known to the team
   - I did not consider discussion necessary
   - Yes

Please continue to next page.
25. Did you recommend follow-up?

- No
- Yes

Who did you recommend do the follow-up?
- Yourself
- GP
- Dermatologist
- Surgeon
- Other  Please specify. __________

How frequently will follow-up be done initially?
At intervals of ____ months.

Please give information on any referrals.

**Referrals**

Please give us the names and addresses of any other doctors to whom you referred this patient for melanoma management.

**Surgeon**

________________________________________

**Dermatologist**

________________________________________

**Medical oncologist**

________________________________________

**Radiation oncologist**

________________________________________

**Other doctor** (Please state specialty if applicable)

________________________________________

Who is this patient’s usual family doctor?
*Please give name and contact details.*

________________________________________

________________________________________

*This is the end of the questionnaire.*

Thank you for your help.
1. TITLE AND SUMMARY OF PROJECT

1. Title

What is the formal title of this research proposal?
The cost effectiveness of managing individuals at high risk of melanoma in a High Risk Clinic, compared with standard care.

What is the short title / acronym of this research proposal (if applicable)?

2. Description of the project in plain language

Give a concise and simple description (not more than 400 words), in plain language, of the aims of this project, the proposal research design and the methods to be used to achieve those aims.

The aim of this study is to determine if it is cost effective from the perspective of the Australian health system to manage individuals considered at high risk of melanoma, in a specialised setting i.e. a high risk clinic, compared with standard care. A clinic for individuals at high risk of melanoma was established at Royal Prince Alfred Hospital (RPAH), Sydney in 2006 with the aim of managing individuals at high risk more efficiently. It is hypothesized that melanomas will be detected earlier and there will be less excisions with a closely managed surveillance program. The second objective is to look at this question from the societal perspective.

The results will be calculated from a modeled comparison between individuals managed through a ‘High Risk Clinic’ surveillance model and those who experience standard care in NSW. Data to estimate the health care costs and outcomes from a specialized clinic will come from individuals attending the high risk clinic at RPAH. Data to estimate the health care costs and outcomes of ‘standard care’ will be taken from high risk individuals in the The 45 and Up study and the Melanoma Patterns of Care Study. The 45 and Up Study dataset will be linked with Medicare Benefits Schedule data at the Sax Institute, and also by The Centre for Health Record Linkage (CHeReL) with data from the Central Cancer Registry and Admitted Patient Data Collection. Data from another high risk cohort in the MPOC Melanoma patterns of Care study, (initiated by the Melanoma Network) will supplement the standard care model. To determine cost effectiveness, a Markov Model (Treeage Pro 2011 Williamstown USA) will be utilized. The model will simulate outcomes based on the natural history of melanoma and will calculate costs and outcomes of surveillance and treatment.

This research will provide evidence to allow the evaluation of both costs and benefits of the high risk clinic model and will have direct policy implication for the management of individuals at high risk of melanoma in Australia. Results will be presented using standard outcomes (i.e. cost per life year saved and cost per quality adjusted life year) allowing comparison of cost effectiveness to be made with other government funded health interventions.

2. RESEARCHERS / INVESTIGATORS

2. Principal researcher(s) / investigator(s)
Principal researcher / investigator 1

Title: Forename/Initials: Surname:
Ms Caroline Watts

Mailing Address: QE II Research Building D02

Suburb/Town: University of Sydney
State: NSW
Postcode: 2006
Country: Australia
Organisation: The University of Sydney
Department*: School of Public Health -Sydney medical School
Position: PhD student
E-mail: caroline.watts@sydney.edu.au
Phone (BH):
Phone (AH)*:
Mobile*:
Pager*:
Fax: 0291141946

Is this person the contact person for this application? ○ Yes ○ No

Summary of qualifications and relevant expertise
BA (Hons), MPH The MPH contained significant components of study in epidemiology and biostatistics. The thesis component of her MPH was a willingness to pay study in which 1900 participants were recruited and answered questions about their perceptions of risk and willingness to pay.

Please declare any general competing interests
Nil

Name the site(s) for which this principal researcher / investigator is responsible.
N/A

Describe the role of the principal researcher / investigator in this project.
Organise, collate, analyse data
Write up the research findings

Is the principal researcher a student? ○ Yes ○ No

What is the educational organisation, faculty and degree course of the student?

Organisation: The University of Sydney
Faculty: Medicine
Degree course: PhD

Is this research project part of the assessment of the student? ○ Yes ○ No

Is the student’s involvement in this project elective or compulsory? ○ Elective ○ Compulsory

What training or experience does the student have in the relevant research methodology?
Caroline Watts has been involved in melanoma research for seven years, working as both a research assistant, and as a project manager, and has an understanding of the issues surrounding melanoma diagnosis and treatment. As the thesis component of her Master of Public Health degree she carried out an economic evaluation of the willingness to pay for Hepatitis A vaccine of 1,900 travelers in Hong Kong. She has participated in a SAS (Statistical Analysis Software) programming course and will complete the Introductory Analysis of Linked Data Course at the University of Sydney.

What training has the student received in the ethics of research?
Caroline Watts has experience with familial research database and family cancer Registers and has experience in protocol development and writing guidelines for the operation of research database and familial registers. She has worked as a research assistant and research interviewer and is aware of the importance of issues around study design and implementation, consent, confidentiality, data.
Describe the supervision to be provided to the student.

Caroline Watts is supervised by Dr Anne Cust, Dr Rachael Morton, Professor Graham Mann and Professor Scott Menzies. The team has expertise in Melanoma epidemiology and health economics. The supervisors meet regularly with Caroline Watts to provide guidance and advice where appropriate.

How many supervisors does the student have? 4

**Supervisor 1**

*Provide the name, qualifications, and expertise, relevant to this research, of the students' supervisor.*

Title: Dr
First Name: Anne
Surname: Cust
Summary of qualifications and relevant expertise

PhD Usyd, MPH(Hons) Usyd, BSc UQ, BA UQ

Dr Cust has been the chief investigator on several grants and fellowships (NHMRC #566946 and #520016, Victorian Cancer Agency #ECSG07_010, Cancer Institute NSW 10/ECF/2-06, Cure Cancer Australia #567001) to investigate genetic and environmental risk factors for melanoma and to determine the risk of melanoma for carriers of inherited genetic mutations.

**Supervisor 2**

*Provide the name, qualifications, and expertise, relevant to this research, of the students' supervisor.*

Title: Professor
First Name: Graham
Surname: Mann
Summary of qualifications and relevant expertise

MBBS PhD

Graham Mann is a Professor in Medicine at the University of Sydney at the Westmead Millennium Institute and Melanoma Institute Australia

He helps lead a multidisciplinary melanoma research program. His research ranges from from population-based studies of genetic and environmental susceptibility to melanoma, to psychosocial aspects of melanoma risk, molecular markers of diagnosis, prognosis and response to treatment.

**Supervisor 3**

*Provide the name, qualifications, and expertise, relevant to this research, of the students' supervisor.*

Title: Dr
First Name: Rachael
Surname: Morton
Summary of qualifications and relevant expertise

PhD Usyd, MScMed (Clin Epi)(Hons) Usyd, Grad Dip (Renal Nursing) RMIT, B Nursing Usyd

Rachael is a research fellow in Health economics, School of Public Health, University of Sydney. Rachael has developed epidemiological studies for the Melanoma Patterns of Care Study, and has conducted cost effective analysis of surgical outcomes for the Melanoma Institute Australia. She teaches Health Economic Evaluation in the Master of Public Health degrees at Sydney University.

**Supervisor 4**

*Provide the name, qualifications, and expertise, relevant to this research, of the students' supervisor.*

Title: Professor
First Name: Scott
Surname: Menzies
Summary of qualifications and relevant expertise

MBBS PhD

Scott Menzies is the Director of Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital, Camperdown.

**Principal researcher / investigator 2**

Title: Forename/Initials: Surname:
Dr Anne Cust

Mailing Address: QE II Research Building D02
A high risk cohort from the Melanoma Patterns of Care study will be defined, or post research access to services, equipment or ‘standard care’ group for comparison. Data from the Melanoma Patterns of Care Study (2) will be used to define the high risk cohort.

For how long will the information be stored after the completion of the project and why has this period been chosen?

Describe what steps, if any, will be taken to ensure that decisions about participation in the research do not impair a participant’s decision to continue in the research. This question aims to assist you and the HREC to identify and address ethical issues that are likely to arise in your research.

The aims of the research and the research question and/or hypotheses, where appropriate.

Anticipated start date: 01/06/2012

This audit is to examine what follow-up care is received by the patient and the impact of follow-up care on patient outcomes (i.e. cost per life year saved and cost per quality adjusted life year) allowing comparison of cost and outcomes (i.e. cost per life year saved and cost per quality adjusted life year). Results based on treatment costs and outcomes will compare Breslow depth at diagnosis, stage at diagnosis, and excision rates. The link between excision, Breslow depth at diagnosis, and melanoma mortality will be explored.

Do privacy guidelines need to be applied in the ethical review of this proposal?

Name/description of the database

The aim of this project is to compare excision rates in a high risk clinic where lesions are monitored closely and those in a general practice setting where lesions are diagnosed at time of excision. Melanomas will be detected earlier and there will be less excisions in a high risk clinic where lesions are monitored closely.

What is the short title/acronym of this research proposal (if applicable):

1. AIHW. Cancer in Australia 2010: an overview. Cancer Series no 60 2010;Cat. no. CAN 56.
2. Victorian Cancer Agency #ECSG07_010, Cancer Institute NSW 10/ECF/2-06, Cure Cancer Australia #567001 to investigate genetic and environmental risk factors for melanoma and to determine the risk of melanoma for carriers of inherited genetic mutations.

Please declare any general competing interests

None

Name the site(s) for which this principal researcher/investigator is responsible.

Sax Institute

The University of Sydney

Describe the role of the principal researcher/investigator in this project.

Principal supervisor for Caroline Watts

Oversee project, assist with study design and methodology, review data analysis and final report

Is the principal researcher a student?

Yes

No

Principal researcher/investigator 3

Title: Professor

Forename/Initials: Graham

Surname: Mann

Mailing Address: Westmead Institute for Cancer Research

PO Box 412

Darcy Road

Suburb/Town: Westmead

State: NSW

Postcode: 2145

Country: Australia

Organisation: The University of Sydney

Department*: Westmead Institute for Cancer Research, Westmead Millennium Institute

Associate Dean Research, Sydney Medical School Chair, University of Sydney Cancer Research Network Deputy Director, Westmead Institute for Cancer Research, WMI and Melanoma Institute Australia

E-mail: graham.mann@sydney.edu.au

Phone (BH): 9845 9056

Phone (AH)*: 0404 741308
Submission Code Date: 25/05/2012 Reference: 11:36:54

Pager*: 9845 9102

Fax: 9845 9102

Is this person the contact person for this application?
☐ Yes  ☐ No

Summary of qualifications and relevant expertise
MBBS PhD

Professor Mann helps lead a multidisciplinary melanoma research program funded by the National Health and Medical Research Council and Cancer Institute NSW, with teams across the University of Sydney and at the Queensland Institute of Medical Research. These programs range from from population-based studies of genetic and environmental susceptibility to melanoma, to psychosocial aspects of melanoma risk, molecular markers of diagnosis, prognosis and response to treatment.

Please declare any general competing interests
None

Name the site(s) for which this principal researcher / investigator is responsible.
None

Describe the role of the principal researcher / investigator in this project.
Co-supervisor for Caroline Watts. Assist with study design and methodology. Will supervise data analysis and with review of final report.

Is the principal researcher a student? ☐ Yes  ☐ No

Principal researcher / investigator 4
Title: Forename/Initials: Surname:
Dr Rachael Morton

Mailing Address: Room 315A Edward Ford Building

Suburb/Town: The University of Sydney
State: NSW
Postcode: 2006
Country:
Organisation: The University of Sydney
Department*: School of Public Health
Position: Research Fellow- Economics
E-mail: rachael.morton@sydney.edu.au
Phone (BH): 9036 5459
Phone (AH)*:
Mobile*:
Pager*:
Fax: 9351 5049

Is this person the contact person for this application?
☐ Yes  ☐ No

Summary of qualifications and relevant expertise
PhD Usyd, MScMed (Clin Epit)(Hons)Usyd, Grad Dip (Renal Nursing) RMIT, B Nursing Usyd

Rachael is a research fellow in Health economics, School of Public Health, University of Sydney. Rachael has developed epidemiological studies for the Melanoma Patterns of Care Study, and has conducted cost effective analysis of surgical outcomes for the Melanoma Institute Australia. She teaches Health Economic Evaluation in the Master of Public Health degrees at Sydney University.

Please declare any general competing interests
None

Name the site(s) for which this principal researcher / investigator is responsible.
The University of Sydney

Describe the role of the principal researcher / investigator in this project.
Co-supervisor for Caroline Watts. Assist with study design and methodology. Will supervise data analysis and with review of final report.
3. Associate Researcher(s) / investigator(s)

How many known associate researchers are there? (You will be asked to give contact details for these associate researchers / investigators)

Do you intend to employ other associate researchers / investigators?  

<table>
<thead>
<tr>
<th>Associate Researcher / Investigator 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title: Forename/Initials: Surname:</td>
</tr>
<tr>
<td>Dr Timothy Dobbins</td>
</tr>
<tr>
<td>Mailing Address: Room 210, QE II Research Institute (DO2)</td>
</tr>
</tbody>
</table>

Suburb/Town: University of Sydney
State: NSW
A cohort of individuals at high risk of melanoma will be selected from 1. The high risk clinic at RPA, 2. the 45 and Up Study and 3. Tucker MA, Fraser MC, Goldstein AM, Elder DE, Guerry DP, Organic SM. Risk of melanoma and other cancers in Sydney Catalyst Top.

The clinic was established in 2006. Information from the comparator group will be obtained from high risk non surveillance groups. Studies have shown regular surveillance of high risk groups assists with early effectiveness ratio of expenditure per quality adjusted life year will also be calculated ensuring that outcomes and benefits of the project will be linked using the Master linkage key via the CHeReL. Data will have an identifying Project Person Number (PPN) or Benefits Schedule data at the Sax Institute, and also by The Centre for Health Record Linkage (CHeReL) with data.

Benefits Schedule data at the Sax Institute, and also by The Centre for Health Record Linkage (CHeReL) with data and from the 45 and Up Study will provide a unique opportunity to identify a cohort of individuals at high risk of melanoma and from the 45 and Up Study will provide a unique opportunity to identify a cohort of individuals at high risk of melanoma and information about the effectiveness ratio of expenditure per quality adjusted life year will also be calculated ensuring that outcomes and benefits of the project will be linked using the Master linkage key via the CHeReL. Data will have an identifying Project Person Number (PPN) or Benefits Schedule data at the Sax Institute, and also by The Centre for Health Record Linkage (CHeReL) with data.

Results based on treatment costs and outcomes will compare Breslow depth at diagnosis, adjusted life year. Results based on treatment costs and outcomes will compare Breslow depth at diagnosis, adjusted life year. Results based on treatment costs and outcomes will compare Breslow depth at diagnosis, adjusted life year. Results based on treatment costs and outcomes will compare Breslow depth at diagnosis, adjusted life year. Results based on treatment costs and outcomes will compare Breslow depth at diagnosis, adjusted life year. Results based on treatment costs and outcomes will compare Breslow depth at diagnosis, adjusted life year. Results based on treatment costs and outcomes will compare Breslow depth at diagnosis, adjusted life year. Results based on treatment costs and outcomes will compare Breslow depth at diagnosis, adjusted life year.
5. Other personnel relevant to the research project

5a. How many known other people will play a specified role in the conduct of this research project?
0

5b. Describe the role, and expertise where relevant (e.g. counsellor), of these other personnel.

5c. Is it intended that other people, not yet known, will play a specified role in the conduct of this research project?

   ○ Yes  ○ No

6. Certification of researchers / investigators

6a. Are there any relevant certification, accreditation or credentialing requirements relevant to the conduct of this research?

   ○ Yes  ○ No

7. Training of researchers

7a. Do the researchers / investigators or others involved in any aspect of this research project require any additional training in order to undertake this research?

   ○ Yes  ○ No

3. RESOURCES

Project Funding / Support

1. Indicate how the project will be funded?

   Type of funding.

   [Please note that all fields in any selected funding detail column (with the exception of the code) will need to be completed.]

   Funding
<table>
<thead>
<tr>
<th>Confirmed or Sought?</th>
<th>Confirmed</th>
<th>Sought</th>
<th>Not Sought</th>
</tr>
</thead>
<tbody>
<tr>
<td>External Competitive Grant</td>
<td>○ Confirmed</td>
<td>○ Sought</td>
<td>○ Not Sought</td>
</tr>
<tr>
<td>Amount of funding $38,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal Competitive Grant</td>
<td>○ Confirmed</td>
<td>○ Sought</td>
<td>○ Not Sought</td>
</tr>
<tr>
<td>Amount of funding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sponsor</td>
<td>○ Confirmed</td>
<td>○ Sought</td>
<td>○ Not Sought</td>
</tr>
<tr>
<td>Amount of funding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>By Researchers Department or Organisation</td>
<td>○ Confirmed</td>
<td>○ Sought</td>
<td>○ Not Sought</td>
</tr>
<tr>
<td>Amount of funding $68,580</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**1a. External Competitive Grant**

<table>
<thead>
<tr>
<th>Name of Grant / Sponsor</th>
<th>Sydney Catalyst Top- Up Scholar Award</th>
</tr>
</thead>
<tbody>
<tr>
<td>Code (optional)</td>
<td></td>
</tr>
<tr>
<td>Detail in kind support</td>
<td>Sydney Catalyst Top-Up scholar award $38,000. Payment of Sydney Catalyst award pending until ethics approval.</td>
</tr>
<tr>
<td>Indicate the extent to which the scope of the grant and the scope of this HREC application are aligned:</td>
<td>Sydney Catalyst funding for data from the 45 and Up study (payment pending until ethics approval). Study described in ethics application is completely aligned with grant application</td>
</tr>
</tbody>
</table>

**1b. Internal Competitive Grant**

<table>
<thead>
<tr>
<th>Name of Grant / Sponsor</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Code (optional)</td>
<td></td>
</tr>
<tr>
<td>Detail in kind support</td>
<td></td>
</tr>
<tr>
<td>Indicate the extent to which the scope of the grant and the scope of this HREC application are aligned:</td>
<td></td>
</tr>
</tbody>
</table>

**1c. Sponsor**

<table>
<thead>
<tr>
<th>Name of Grant / Sponsor</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Code (optional)</td>
<td></td>
</tr>
<tr>
<td>Detail in kind support</td>
<td></td>
</tr>
<tr>
<td>Indicate the extent to which the scope of the grant and the scope of this HREC application are aligned:</td>
<td></td>
</tr>
</tbody>
</table>

**1d. By Researchers Department or Organisation**

<table>
<thead>
<tr>
<th>Name of Grant / Sponsor</th>
<th>Cancer Institute NSW Early Career Development Fellowship award to Dr Anne Cust, awarded through the Sydney Medical School was awarded to Caroline Watts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Code (optional)</td>
<td>Post graduate scholarship $68,580 Scholarship for research into Cancer Epidemiology (Melanoma)</td>
</tr>
<tr>
<td>Detail in kind support</td>
<td>Study described in ethics application is completely aligned with grant application</td>
</tr>
<tr>
<td>Indicate the extent to which the scope of the grant and the scope of this HREC application are aligned:</td>
<td>Study described in ethics application is completely aligned with grant application</td>
</tr>
</tbody>
</table>

**2. How will you manage a funding shortfall. (if any)**

Not expecting funding shortfall

**3. Will the project be supported in other ways eg. in-kind support/equipment by an external party eg. sponsor?**

- [ ] Yes  
- [x] No

**4. Is this a study where capitation payments are to be made, and will participants be made aware of these payments to clinicians or researchers / investigators?**

No

**Duality of Interest**

**5. Describe any commercialisation or intellectual property implications of the funding/support arrangement.**
6. Does the funding/support provider(s) have a financial interest in the outcome of the research?

   ○ Yes   ○ No

7. Does any member of the research team have any affiliation with the provider(s) of funding/support, or a financial interest in the outcome of the research?

   ○ Yes   ○ No

8. Does any other individual or organisation have an interest in the outcome of this research?

   ○ Yes   ○ No

9. Are there any restrictions on the publication of results from this research?

   ○ Yes   ○ No

4. PRIOR REVIEWS

Ethical Review

Some HRECs may require researchers to provide information additional to that contained in a NEAF proposal. For this reason, it is prudent to check whether the HRECs to whom you propose to submit this proposal require additional information.

Duration and location

1. In how many Australian sites, or site types, will the research be conducted?

   2

2. In how many overseas sites, or site types, will the research be conducted?

   0

3. Provide the following information for each site or site type (Australian and overseas, if applicable) at which the research is to be conducted

   1
   Site / Site Type Name: Sax Institute
   Site / Site Type Location: Level 2
   10 Quay Street
   Haymarket
   NSW 2000

   2
   Site / Site Type Name: Sydney University
   Site / Site Type Location: Room 202
   QE II Research Building
   Sydney University
   NSW 2006

   3
4. Provide the start and finish dates for the whole of the study including data analysis
   Anticipated start date: 01/06/2012 (dd/mm/yyyy)
   Anticipated finish date: 30/06/2014 (dd/mm/yyyy)

5. Are there any time-critical aspects of the research project of which an HREC should be aware?
   Yes
   No

   Describe the time-critical aspects:
   Quote for use of the 45 and Up study resource expires 6th December 2012. Analysis of MBS data must be done at the Sax Institute in accordance with their governance requirements. Data license is valid for 1 year.

6. To how many Australian HRECs (representing site organisations or the researcher’s / investigator’s organisation) is it intended that this research proposal be submitted?
   1
   A list of NHMRC registered Human Research Ethics Committees (HRECs), along with their institutional affiliations and contact details is available on the NHMRC website at the following web address: http://www.nhmrc.gov.au/health_ethics/hrecs/overview.htm#d.

7. HRECs

   HREC 1

   Name of HREC:
   NSW Population and Health Service Research Ethics Committee (EC00410)

   Provide the start and finish dates for the research for which this HREC is providing ethical review:
   Anticipated start date or date range: 01/04/2012 (dd/mm/yyyy)
   Anticipated finish date or date range: 01/06/2014 (dd/mm/yyyy)

   For how many sites at which the research is to be conducted will this HREC provide ethical review?
   2

   Site 1

   Name of Site: Sax Institute

   Principal Researcher 1

   Principal Researcher Name: Ms Caroline Watts

   Principal Researcher 2

   Principal Researcher Name: Dr Anne Cust
Site 2

Name of Site: Sydney University

Principal Researcher 1

Principal Researcher Name: Ms Caroline Watts

Associate Researcher 1

Associate Researcher Name: Dr Anne Cust

Associate Researcher 2

Associate Researcher Name: Dr Rachael Morton

Associate Researcher 3

Associate Researcher Name: Professor Graham Mann

Associate Researcher 4

Associate Researcher Name: Professor Scott Menzies

Associate Researcher 5

Associate Researcher Name: Dr Timothy Dobbins

Associate Researcher 6
Provide details of the review and the outcome. A copy of the letter / notification, where available, should be attached to this application.

Protocol was submitted to Sydney Catalyst for a top up scholar award. The project was awarded funding for data linkage, with funding dependent on ethics approval.

Protocol was submitted to investigators of Melanoma Patterns Of Care study for permission to use de-identified data and permission given for use of data pertaining to high risk individuals, pending ethics approval. An application was made to the 45 and Up study for a quote to use de-identified study data. Approval for data linkage has been granted subject to ethics approval.

5. PROJECT

1. Type of Research

Tick as many of the following ‘types of research’ as apply to this project. Your answers will assist HRECs in considering your proposal. A tick in some of these boxes will generate additional questions relevant to your proposal (mainly because the National Statement requires additional ethical matters to be considered), which will appear in Section 4 of NEAF.

The project involves:

☐ Research using qualitative methods
☐ Research using quantitative methods, population level data or databanks, e.g. survey research, epidemiological research
☐ Clinical research
☐ Research involving the collection and / or use of human samples
☐ Genetic testing/research
☐ A cellular therapy
☐ Research on workplace practices or possibly impacting on workplace relationships
☐ Research conducted overseas involving participants
☐ Research involving ionising radiation
☐ Research involving gametes or use or creation of embryos
☐ None of the above

Does the research involve limited disclosure to participants?

☐ Yes    ☐ No

Are the applicants asking the HREC / review body to waive the requirement of consent?

☐ Yes    ☐ No

Research plan

2. Describe the theoretical, empirical and/or conceptual basis, and background evidence, for the research proposal, e.g. previous studies, anecdotal evidence, review of literature, prior observation, laboratory or animal studies.

Cutaneous melanoma is the fourth most common cancer in both men and women in Australia and the third most common cancer in NSW(1). From 2002-2007 the incidence of melanoma in Australia has steadily increased, and this trend is expected to continue(2). It has been long recognized that certain groups in the population have a greater chance of developing melanoma than the general population(3,4). Some factors that place individuals at high risk for developing melanoma include familial predisposition(5), a previous personal history of melanoma(6) and the presence of clinically dysplastic nevi(7) and many melanocytic nevi(8), which may be classified as dysplastic nevus...
syndrome (DNS), familial melanoma in the presence of DNS, atypical moles (FAMMM syndrome) or atypical mole syndrome (AMS)(9).

Population screening is currently not recommended in Australia10. Recommendations for General Practitioners are to assess their patient’s risk of melanoma and develop surveillance programs accordingly(10). Early detection is a primary factor in survival and the rationale for screening individuals at high, risk(11,12). Opportunistic screening or targeting high risk groups for screening have been shown to be effective in diagnosing melanomas earlier than in non surveillance groups(13,14). Studies have shown regular surveillance of high risk groups assists with early detection(13,15,16).

The introduction of a specialised clinic through funding from Cancer Institute NSW translational grant, at Royal Prince Alfred Hospital in 2006 was a major initiative to improve the care of individuals at high risk of melanoma in NSW. In 2012, the high risk clinic model will be expanded to three more centres in NSW. The intervention group will be modelled on data from the High Risk Clinic.

The availability of two unique data sets provides a means of addressing previous research impediments of defining and measuring a suitable ‘standard care’ group for comparison. Data from the Melanoma Patterns of Care Study and from the 45 and Up Study will provide a unique opportunity to identify a cohort of individuals at high risk of melanoma that were managed with ‘standard care.’ The Melanoma Patterns of Care Study will provide information about medical management of melanoma, and linked data from respondents in The 45 and Up Study will provide additional information about individual costs and outcomes related to both melanoma and non-melanoma excisions. The 45 and Up Study data will be linked at the SAX Institute to the Medicare Benefits Schedule data and through the Centre for Health Record Linkage (CheReL) to the Central Cancer Registry and the Admitted Patient Data Collection.

The evaluation of the high-risk clinic model has direct implications for policy and health outcomes for individuals at high risk of melanoma in Australia. Evidence of the costs per melanoma excised, and numbers of excisions per melanoma detected, have direct implications for the overall costs incurred by the health system. An incremental cost-effectiveness ratio of expenditure per quality adjusted life year will also be calculated ensuring that outcomes include issues such as quality of life. Guidelines are varied in the recommendations about the identification and care of individuals at high risk of melanoma. There is a need to define and measure outcomes to improve the quality of information around surveillance and issues such as quality of life and cost effectiveness also need to be considered(17). Results will be presented using standard outcomes (i.e. cost per life year saved and cost per quality adjusted life year) allowing comparison of cost effectiveness to be made with other government funded health interventions.

References:
1. AIHW. Cancer in Australia 2010: an overview. Cancer Series no 60 2010;Cat. no. CAN 56. (Canberra: AIHW).
3. State the aims of the research and the research question and/or hypotheses, where appropriate.

The aim of this research project is to determine if it is cost effective to manage individuals considered at high risk of melanoma in a specialised setting i.e. a high risk clinic compared with standard care, from an Australian health system perspective. A secondary aim is to examine this question from a societal perspective.

The intervention group will be modeled on data from individuals attending the high risk clinic at Royal Prince Alfred hospital. The clinic was established in 2006. Information from the comparator group will be obtained from high risk individuals selected from the Melanoma Patterns of Care study and the 45 and Up study. It is hypothesized that melanomas will be detected earlier and there will be less excisions in a high risk clinic where lesions are monitored frequently.

Results will be presented as an incremental cost effectiveness ratio of $A per year saved and $A per quality adjusted life year. Results based on treatment costs and outcomes will compare Breslow depth at diagnosis, number of excisions per melanoma detected, quality of life outcomes, expected morbidity and survival. The societal perspective will include a broader analysis of quality of life assessment, patient out-of-pocket expenses and productivity losses.

4. Has this project been undertaken previously?

☐ Yes  ☐ No

Benefits/Risks

In answering the following questions (Q 5 – 11) please ensure that you address all issues relevant to the type of participants that will be involved in your research project. Refer for guidance to relevant chapters of the National Statement.

5. Does the research involve a practice or intervention which is an alternative to a standard practice or intervention?

☐ Yes  ☐ No

7. What expected benefits (if any) will this research have for the wider community?

The evaluation of the cost effectiveness of the high-risk clinic model from both a health system and societal perspective has direct implications for policy and health outcomes for individuals at high risk of melanoma in Australia. Evidence of the costs per melanoma excised, and numbers of excisions per melanoma detected, have direct implications for the overall costs incurred by the health system. Results will be presented using standard outcomes (i.e. cost per life year saved and cost per quality adjusted life year) allowing comparison of cost effectiveness to be made with other government funded health interventions.

8. What expected benefits (if any) will this research have for participants?

An incremental cost-effectiveness ratio of expenditure per quality adjusted life year saved will also be calculated ensuring that outcomes include issues such as quality of life. Potentially health policy would be guided by this research in the provision of a model of care for individuals at high risk of melanoma

9. Are there any risks to participants as a result of participation in this research project?

☐ Yes  ☐ No
10. Explain how the likely benefit of the research justifies the risks of harm or discomfort to participants.

None

11. Are there any other risks involved in this research? eg. to the research team, the organisation, others

☐ Yes  ☐ No

12. Is it anticipated that the research will lead to commercial benefit for the investigator(s) and or the research sponsor(s)?

☐ Yes  ☐ No

16. Is there a risk that the dissemination of results could cause harm of any kind to individual participants - whether their physical, psychological, spiritual, emotional, social or financial well-being, or to their employability or professional relationships - or to their communities?

☐ Yes  ☐ No

17. What mechanisms do the researchers / investigators intend to implement to monitor the conduct and progress of the research project?

The PhD candidate has fortnightly meetings with her supervisors to discuss methods, findings and review her progress.

The researcher will be required to attend the Sax Institute for linkage from the 45 and Up data to Medicare Australia as per the conditions of use. Analysis of other linked datasets co-ordinated through the CHeReL linking the 45 and Up study to the NSW Central Cancer Registry and Admitted Patients Hospital Data Collection will be done at the University of Sydney.

Annual reports will be provided to Sydney catalyst as required through receipt of the scholar award.

6. PARTICIPANTS

1. Research participants

The National Statement identifies the need to pay additional attention to ethical issues associated with research involving certain specific populations.

This question aims to assist you and the HREC to identify and address ethical issues that are likely to arise in your research, if its design will include one or more of these populations. Further, the National Statement recognizes the cultural diversity of Australia’s population and the importance of respect for that diversity in the recruitment and involvement of participants. Your answer to this question will guide you to additional questions (if any) relevant to the participants in your study.

Tick as many of the following 'types of research participants' who will be included because of the project design, or their inclusion is possible, given the diversity of Australia’s population. If none apply, please indicate this below.

If you select column (a) or (b), column (c) will not apply.

<table>
<thead>
<tr>
<th>The participants who may be involved in this</th>
<th>a) Primary</th>
<th>b) Probable</th>
<th>c) Design</th>
</tr>
</thead>
</table>

Commonwealth of Australia

AU/1/FD7D013

232
If you select column (a) or (b), column (c) will not apply.

- People whose primary language is other than English (LOTE)
- Women who are pregnant and the human foetus
- Children and/or young people (ie. <18 years)
- People in existing dependent or unequal relationships
- People highly dependent on medical care
- People with a cognitive impairment, an intellectual disability or a mental illness
- Aboriginal and/or Torres Strait Islander peoples
- People who may be involved in illegal activity
- None apply

You have indicated that it is probable that
- People whose primary language is other than English (LOTE)
- Women who are pregnant and the human foetus
- People in existing dependent or unequal relationships
- People highly dependent on medical care
- People with a cognitive impairment, an intellectual disability or a mental illness
- Aboriginal and/or Torres Strait Islander peoples
- People who may be involved in illegal activity

may be coincidentally recruited into this project. The National Statement identifies specific ethical considerations for these groups(s).

Please explain how you will address these considerations in your proposed research. These population groups may be in the cohort of individuals who fit the criteria for high risk of melanoma and who have had a reported melanoma. However all data provided will be in a deidentified form so there is negligible risk to individuals.

2. How many participant groups are involved in this research project?
3

3. What is the expected total number of participants in this project at all sites?
2,300

4. Groups

Group 1

| Group name for participants in this group: | High Risk Clinic (HRC) participants |
| Expected number of participants in this group: | 300 |
| Age range: | >18 |
Other relevant characteristics of this participant group:
At high risk of melanoma.
A. Dysplastic nevus syndrome (>100 Naevi, > 5 dysplastic naevus, > 1 dysplastic naevus 8 mm in diam) and history of melanoma
B. Personal history > 2 melanoma
C. Personal history of melanoma and > 3 1st or 2nd degree relatives with melanoma
D. CDKN2A or CDK4 melanoma prone gene mutation

Why are these characteristics relevant to the aims of the project?
Estimate health outcomes and resource use of the high risk group to determine cost of a high risk clinic to the health system
1. With the written consent of the participants the researcher intends to observe HRC over 3 weeks. Over this period approximately 50 skin examinations could be observed. Rationale for observing clinic is to cost out the time per visit and understand how the clinic operates.
2. A survey of first 100 participants as these records would have the most information and hopefully avoid selection bias. Rational for looking at the records is to examine what follow-up happens outside the clinic, morbidity related to excisions, other procedures related to a melanoma diagnosis, and hospital admissions. This audit would include RPA hospital records where appropriate. The aim is to document and cost the outcomes.
3. To identify and measure and cost the surveillance outcomes of the high risk clinic participants. De-identified data set for 300 participants will provide baseline data about individuals at high risk of melanoma and information about the management of melanoma and non melanoma excisions.

Group 2

Group name for participants in this group: Melanoma Patterns of care Study
Expected number of participants in this group: 1380
Age range: >18 years

Other relevant characteristics of this participant group:
Confirmed melanoma between October 2006 and October 2007. A cohort of individuals at higher risk than the general population as defined by
1. A report from a treating clinician of a patient who has had two melanomas excised
2. A report from a treating clinician of a patient with lots of moles and a melanoma excised
3. A report from a treating clinician of a patient with a family history of melanoma in a blood relative and a melanoma excised

Why are these characteristics relevant to the aims of the project?
A cohort of individuals at high risk of melanoma who have been treated in the community are a suitable comparator will provide baseline data about individuals at high risk of melanoma and information about the management of melanoma excisions.

Group 3

Group name for participants in this group: The 45 and Up study resource
Expected number of participants in this group: 730
Age range: > 45 years

Other relevant characteristics of this participant group:
The 45 and Up study is a long term health cohort health study of men and women over 45 years living in NSW. We define ‘high risk’ in The 45 and Up Study as
1. An individual with a self-report of melanoma and a report of melanoma in two blood relatives.

Through the CheReL, linkage with Central Cancer Registry will confirm the diagnosis of melanoma and Admitted Patient Data Collection to collect information on health care outcomes and cost. Through the Sax Institute this data will be linked with Medicare Australia to access data on excisions, treatment costs, out of pocket costs and distance travelled from home to the melanoma centre.

Why are these characteristics relevant to the aims of the project?
A cohort of individuals at high risk of melanoma who have been treated in the community are a suitable comparator and will provide baseline data about individuals at high risk of melanoma and information about the management of melanoma and non melanoma excisions.

Participant experience

6. Provide a concise detailed description, in not more than 200 words, in terms which are easily understood by the lay reader of what the participation will involve.

This study involves no direct participant participation. All data, are collated data sets from a third party and are de-
A cohort of individuals at high risk of melanoma will be selected from: 1. The high risk clinic at RPA, 2. the 45 and Up study and 3. the Melanoma Patterns of Care Study (MPOC).

1. High risk clinic data set from Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital will be de-identified before it is provided for use in this study.
2. The 45 and Up study cohort will link through the CHeReL, the 45 and Up study with the NSW Central Cancer Registry and the Admitted Patient Data Collection. The 45 and Up Study data will also be linked to Medicare Australia for MBS data at the Sax Institute.
3. A high risk cohort from the Melanoma Patterns of Care study will be de-identified before it is provided for use in this study.

The study is a modelled economic evaluation and individual data is used calculate health outcomes and resource use and costs. The information will reflect collated results only.

Relationship of researchers / investigators to participants

7. Specify the nature of any existing relationship or one likely to rise during the research, between the potential participants and any member of the research team or an organisation involved in the research.

9. Describe what steps, if any, will be taken to ensure that the relationship does not impair participants’ free and voluntary consent and participation in the project.

10. Describe what steps, if any, will be taken to ensure that decisions about participation in the research do not impair any existing or foreseeable future relationship between participants and researcher / investigator or organisations.

11. Will the research impact upon, or change, an existing relationship between participants and researcher / investigator or organisations?

Yes  No

Recruitment

13. What processes will be used to identify potential participants?

14. Is it proposed to ‘screen’ or assess the suitability of the potential participants for the study?

Yes  No

15. Describe how initial contact will be made with potential participants.

16. Do you intend to include both males and females in this study?

Yes  No

What is the expected ratio of males to females that will be recruited into this study and does this ratio accurately reflect the distribution of the disease, issue or condition within the general community?
We would expect to have a representative sample and approximately equal male to female ratio.

17. Is an advertisement, e-mail, website, letter or telephone call proposed as the form of initial contact with potential participants?

☐ Yes  ☐ No

18. If it became known that a person was recruited to, participated in, or was excluded from the research, would that knowledge expose the person to any disadvantage or risk?

☐ Yes  ☐ No

Consent process

19. Will consent for participation in this research be sought from all participants?

☐ Yes  ☐ No

Explain why consent will not be sought from all participants:

This study will use only de-identified data provided by a third party.

Your response to this question must explain why it is impracticable to obtain consent (for example, due to the quantity, age or accessibility of the records).

Do you propose to obtain consent from individual participants for your use of their stored data/samples for this research project?

☐ Yes  ☐ No

Give justification This study will use only de-identified data provided by a third party.
applicable, the reasons for using identifiable or re-identifiable data.

Commonwealth 1
State/Territory 3
Private Sector 2

1
Name of agency / organisation: Sax Institute
Agency Type:
  □ Commonwealth
  □ State/Territory
  □ Private Sector
Name/description of the database: The Sax Institute manages the 45 and Up study, which includes the 45 and Up Study data set and also the Medicare Australia Data (Referred to in 2). The 45 and Up dataset will be linked using the Master linkage key via the CHeReL.
Describe the information that will be collected. List all data items:
The linkage has two stages 1. linkage using identifiable data and 2. analysis of non-identifiable data. Once linkage has been completed, identifiers are removed from the data set by CHeReL and the Sax Institute. Data will have an identifying Project Person Number (PPN) or study number so that data from other linkage studies can be utilised by the CHeReL. Research items for analysis are listed on the attached Data Variable List

The information collected by the research team about participants will be in the following form(s).

[ ] individually identifiable
[ ] re-identifiable
[✓] non-identifiable

2
Name of agency / organisation: Medicare Australia
Agency Type:
  □ Commonwealth
  □ State/Territory
  □ Private Sector
Name/description of the database: The Sax Institute manages the 45 and Up study, which includes the 45 and Up Study data set and also the Medicare Australia Data. MBS data will be accessed according to the governance requirements at The Sax Institute.
Describe the information that will be collected. List all data items:
MBS data items used are held in the master linkage key at the Sax Institute. Linkage will be performed using personally identifiable data with the process conducted at secure facilities by the Sax Institute.
The linkage has two stages 1. linkage using identifiable data and 2. analysis of non-identifiable data. Once linkage has been completed, identifiers are removed from the data set by the Sax Institute. Analysis of the 45 and Up study data set and MBS data by the researcher occurs at the Sax Institute and only collated data can be removed from the Sax Institute. Research items for analysis are listed on the attached Data Variable List

The information collected by the research team about participants will be in the following form(s).

[ ] individually identifiable
[ ] re-identifiable
[✓] non-identifiable
3
Name of agency / organisation: CINSW

Agency Type:
- Commonwealth
- State/Territory
- Private Sector

Name/description of the database
NSW Central Cancer Registry

Describe the information that will be collected. List all data items
The data items are held by CHaRel Master Linkage key. Linkage will be performed using personally identifiable data with the process conducted at secure facilities by the CHaRel.

Research items for analysis are listed on the attached Data Variable List

The information collected by the research team about participants will be in the following form(s).
- [ ] individually identifiable
- [ ] re-identifiable
- [✓] non-identifiable

4
Name of agency / organisation: APDC

Agency Type:
- Commonwealth
- State/Territory
- Private Sector

Name/description of the database
NSW Admitted Patient Data Collection

Describe the information that will be collected. List all data items
The data items are held by CHaRel Master Linkage key. Linkage will be performed using personally identifiable data with the process conducted at secure facilities by the CHaRel.

Research items for analysis are listed on the attached Data Variable List

The information collected by the research team about participants will be in the following form(s).
- [ ] individually identifiable
- [ ] re-identifiable
- [✓] non-identifiable

5
Name of agency / organisation: Melanoma Network Australia
### The information which will be stored at the completion of this project is of the following type(s).

- Cust
- pathological variant
- Melanoma Patterns of Care (MPOC) Study

From the MPOC study, a cohort of adults (de-identified) at high risk of melanoma who had a melanoma diagnosed between Oct 2006 and Oct 2007 will be provided to this study.

#### History of previous melanomas
- Age, sex, postcode
- Record of criteria for inclusion in clinic
- Record of visits
- All records of treatment, excisions and pathology reports associated with surveillance and follow-up will be collected

### The information collected by the research team about participants will be in the following form(s).

- - individually identifiable
- - re-identifiable
- - non-identifiable

### 6

| Name of agency / organisation: | Sydney Melanoma Diagnostic Centre |
| Agency Type: | Commonwealth |
| Name/description of the database: | High Risk Clinic |
| Describe the information that will be collected. List all data items | History of previous melanomas Age, sex, postcode Record of criteria for inclusion in clinic Record of visits All records of treatment, excisions and pathology reports associated with surveillance and follow-up will be collected |

### The information collected by the research team about participants will be in the following form(s).

- - individually identifiable
- - re-identifiable
- - non-identifiable

### 7

| Name of agency / organisation: | Melanoma Network |
| Agency Type: | Commonwealth |
| Name/description of the database: | A cohort of individuals who fulfil the criteria of high risk will be selected from The Melanoma Patterns of Care Study (MPOC). History of previous melanomas Age, sex, postcode |
| Describe the information that will be collected. List all data items | Record of criteria for inclusion in MPOC Record of visits |
All records of treatment, excisions and pathology report associated with surveillance and follow-up will be collected.

The information collected by the research team about participants will be in the following form(s).

- [ ] individually identifiable
- [ ] re-identifiable
- [x] non-identifiable

Using information from participants

2. Describe how information collected about participants will be used in this project.

The MPOC data will be used to characterise the population of high risk individuals in NSW. The frequencies of characteristics will be used in the model which is based on the health outcomes and costs for a cohort of individuals at high risk of melanoma. A comparison between standard care and the intervention (those attending a high risk Clinic) will be made to determine the incremental cost effectiveness ratios from both a health system and societal perspective.

Data from the 45 and Up study, MPOC study and High Risk Clinic will be used to examine participants treatment and management, this information will be collated to determine the outcomes and costs associated with surveillance and treatment for melanoma.

Data will be analysed using SAS (statistical analysis software) at the Sax Institute and University of Sydney, and also 'Treeage' software to build and analyse the cost effectiveness model.

3. Will any of the information be used by the research team be in identified or re-identifiable (coded) form?

- [ ] Yes
- [x] No

4. List ALL research personnel and others who, for the purposes of this research, will have authority to use or have access to the information and describe the nature of the use or access. Examples of others are: student supervisors, research monitors, pharmaceutical company monitors.

- Ms Caroline Watts
- Dr Anne Cust
- Dr Rachael Morton
- Professor Graham Mann
- Professor Scott Menzies
- Dr Timothy Dobbins
- Mr Chris Goumas

Storage of information about participants during and after completion of the project

5. In what formats will the information be stored during and after the research project? (eg. paper copy, computer file on floppy disk or CD, audio tape, videotape, film)

Data will be stored securely on a password protected computer in Room 202, Queen Elizabeth Research Building, University of Sydney, using a SAS database and backed up daily on a server managed by the Information and Communications Department at the University of Sydney. Access to the building where the database is stored is restricted to a small number of researchers with a security passcard. The office is locked after hours.

The data will be held on the University server for 7 years after completion of the project. All data files will be deleted after this time.

6. Specify the measures to be taken to ensure the security of information from misuse, loss, or unauthorised access while stored during and after the research project? (eg. will identifiers be removed and at what stage? Will the information be physically stored in a locked cabinet?)
Data will be stored securely on a password protected computer in Room 202, Queen Elizabeth Research Building, University of Sydney, using a SAS database and backed up daily on a server managed by the Information and Communications Department at the University of Sydney. Access to the building where the database is stored is restricted to a small number of researchers with a security passcard. The office is locked after hours. The data will be held on the University server for 7 years after completion of the project. All data files will be deleted after this time.

9. The information which will be stored at the completion of this project is of the following type(s). Tick more than one box if applicable.

- [ ] individually identifiable
- [ ] re-identifiable
- [✓] non-identifiable

10. For how long will the information be stored after the completion of the project and why has this period been chosen?

The data will be held on the server for 7 years after completion of the project. All data files will be deleted after this time. Storage for 7 years will allow sufficient time for any additional analyses or follow-up studies to be conducted.

11. What arrangements are in place with regard to the storage of the information collected for, used in, or generated by this project in the event that the principal researcher / investigator ceases to be engaged at the current organisation?

Should the principal researcher cease to be engaged by the University of Sydney before the completion of the project, a protocol amendment would be submitted to the ethics committee at this time for another researcher to oversee completion of the project. The supervisor Dr Anne Cust would oversee this process facilitating the change of data storage and data access arrangements from the principal researcher to her replacement.

Ownership of the information collected during the research project and resulting from the research project

13. Who is understood to own the information resulting from the research, eg. the final report or published form of the results?

The University of Sydney

14. Does the owner of the information or any other party have any right to impose limitations or conditions on the publication of the results of this project?

- [✓] Yes
- [ ] No

Specify any limitations on publication:
The data custodians and CHeReL will be acknowledged in any publications.
The Sax Institute have requested to review any documents prior to publication.
This research is supported by a Cancer Institute Early Researcher Award to Dr Anne Cust and a Sydney Catalyst Top-Up scholar award which will be acknowledged.

Disposal of the information

15. Will the information collected for, used in, or generated by this project be disposed of at some stage?

- [ ] Yes
- [✓] No

At what stage will the information be disposed?
The data will be held on the University server for 7 years after completion of the project and then all files deleted.
How will information, in all forms, be disposed?
All data files will be deleted after this time.
Reporting individual results to participants and others

16. Is it intended that results of the research that relate to a specific participant be reported to that participant?

- Yes
- No

*Explain/justify why results will not be reported to participants:*
The researchers will not be able to identify participants.

17. Is the research likely to produce information of personal significance to individual participants?

- Yes
- No

18. Will individual participant's results be recorded with their personal records?

- Yes
- No

19. Is it intended that results that relate to a specific participant be reported to anyone other than that participant?

- Yes
- No

20. Is the research likely to reveal a significant risk to the health or well being of persons other than the participant, eg family members, colleagues?

- Yes
- No

21. Is there a risk that the dissemination of results could cause harm of any kind to individual participants - whether their physical, psychological, spiritual, emotional, social or financial well-being, or to their employability or professional relationships - or to their communities?

- Yes
- No

22. How is it intended to disseminate the results of the research? eg report, publication, thesis

The results of this research will contribute to the PhD thesis of Caroline Watts. It is also intended that the results of this research will be published in peer-reviewed journals, and presented at conferences and professional meetings.

23. Will the confidentiality of participants and their data be protected in the dissemination of research results?

- Yes
- No

*Explain how confidentiality of participants and their data will be protected in the dissemination of research results:*
All information used for this research has been provided for use in a de-identified form. Data at a 'group level' will be presented. No individuals will be identifiable.
I/we certify that:

- All information is truthful and as complete as possible.
- I/we have had access to and read the National Statement on Ethical Conduct in Research Involving Humans.
- The research will be conducted in accordance with the National Statement.
- The research will be conducted in accordance with the ethical and research arrangements of the organisations involved.
- The research will be conducted in accordance with the ethical and research arrangements of the organisations involved.
- I/we have consulted any relevant legislation and regulations, and the research will be conducted in accordance with these.
- I/we will immediately report to the HREC anything which might warrant review of the ethical approval of the proposal (NS 2.37), including:
  - serious or unexpected adverse effects on participants;
  - proposed changes in the protocol; and
  - unforeseen events that might affect continued ethical acceptability of the project.
- I/we will inform the HREC, giving reasons, if the research project is discontinued before the expected date of completion (NS 2.38);
- I/we will not continue the research if ethical approval is withdrawn and will comply with any special conditions required by the HREC (NS. 2.45);
- I/we will adhere to the conditions of approval stipulated by the HREC and will cooperate with HREC monitoring requirements. At a minimum annual progress reports and a final report will be provided to the HREC.

**Applicant / Chief Researcher(s) / Principal Researcher(s)**

<table>
<thead>
<tr>
<th>Name and Relationship</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ms Caroline Watts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The University of Sydney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Anne Cust</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The University of Sydney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professor Graham Mann</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The University of Sydney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Rachael Morton</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The University of Sydney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professor Scott Menzies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Royal Prince Alfred Hospital</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Associate Researchers**

<table>
<thead>
<tr>
<th>Name and Relationship</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Timothy Dobbins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The University of Sydney</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Supervisor(s) of student(s)**

<table>
<thead>
<tr>
<th>Project Title (in full):</th>
<th>The cost effectiveness of managing individuals at high risk of melanoma in a High Risk Clinic, compared with standard care.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HREC to which this application is made:</td>
<td></td>
</tr>
<tr>
<td>HREC Reference number:</td>
<td></td>
</tr>
</tbody>
</table>

I/we certify that:

- I/we will provide appropriate supervision to the student to ensure that the project is undertaken in accordance with the undertakings above;
- I/we will ensure that training is provided necessary to enable the project to be undertaken skilfully and ethically.

Dr Anne Cust

<table>
<thead>
<tr>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
</table>

Professor Graham Mann

<table>
<thead>
<tr>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
</table>

Dr Rachael Morton

<table>
<thead>
<tr>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
</table>

Professor Scott Menzies

<table>
<thead>
<tr>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
</table>

**Heads of departments/schools/research organisation**

<table>
<thead>
<tr>
<th>Project Title (in full):</th>
<th>The cost effectiveness of managing individuals at high risk of melanoma in a High Risk Clinic, compared with standard care.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HREC to which this application is made:</td>
<td></td>
</tr>
<tr>
<td>HREC Reference number:</td>
<td></td>
</tr>
</tbody>
</table>

I/we certify that:

- I/we are familiar with this project and endorse its undertaking;
- the resources required to undertake this project are available;
- the researchers have the skill and expertise to undertake this project appropriately or will undergo appropriate training as specified in this application.
Give a concise and simple description (not more than 400 words), in plain language, of the aims of this project, the methods to be used and how the data will be collected (informed consent).

Project Title (in full): The cost effectiveness of managing individuals at high risk of melanoma

The clinic was established in 2006. Information from the comparator group will be obtained from high risk care of individuals at high risk of melanoma. There is a need to define and measure outcomes to improve the quality of care.

Site 1

1c.

2. RESEARCHERS / INVESTIGATORS

Associate Researcher Name: PhD Usyd, MScMed (Clin Epi)(Hons) Usyd, Grad Dip (Renal Nursing) RMIT, B Nursing Usyd

PhD Usyd

MBBS PhD

Graham

Nil

Assist with biostatistical advice and analysis if required

Summary of qualifications and relevant expertise

 QE II Research Building

2. A report from a treating clinician of a patient with lots of moles and a melanoma excised

3. A report from a pathologist stating that a melanoma was excised

4. A pathology report stating the histological grade of a melanoma

5. An oncologist's report stating that a melanoma was excised

6. A pathology report stating the histological grade of a melanoma

7. A pathology report stating the histological grade of a melanoma

8. A pathology report stating the histological grade of a melanoma

1. Recruitment/invitation

Core Attachments

Recruitment/invitation

Participant Information

Consent Form

Peer review

HREC approvals

Attachments which may be required/appropriate

Copy of advertisement, letter of invitation etc

Copy or script for participant

Copy or script for participant, legal guardian or person responsible as appropriate

Copy for participant

Copy for participant

For parent, legal guardian or person responsible as appropriate

For, optional components of the project eg, genetic sub study

Copy of peer review report or grant submission outcome

Copy of outcome of other HREC reviews

Attachments specific to project or participant group

People whose primary language is other than English (LOTE)

People with an intellectual or mental impairment

People highly dependent on medical care

Aboriginal and/or Torres Strait Islander peoples

Attachments which may be required/appropriate

English translation of participant information/consent forms

Information/consent form for legal guardian or person responsible

Information/consent form for legal guardian or person responsible

Evidence of support / permission of elders and/or other appropriate bodies

Participant information elements

Core Elements

Provision of information to participants about the following topics should be considered for all research projects.

<table>
<thead>
<tr>
<th>Core Elements</th>
<th>Issues to consider in participant information</th>
</tr>
</thead>
</table>

11. Attachments

List of Attachments

Core Attachments

Recruitment/invitation

Participant Information

Consent Form

Peer review

HREC approvals

Attachments which may be required/appropriate

Copy of advertisement, letter of invitation etc

Copy or script for participant

Copy or script for participant, legal guardian or person responsible as appropriate

Copy for participant

Copy for participant

For parent, legal guardian or person responsible as appropriate

For, optional components of the project eg, genetic sub study

Copy of peer review report or grant submission outcome

Copy of outcome of other HREC reviews

Attachments specific to project or participant group

People whose primary language is other than English (LOTE)

People with an intellectual or mental impairment

People highly dependent on medical care

Aboriginal and/or Torres Strait Islander peoples

Attachments which may be required/appropriate

English translation of participant information/consent forms

Information/consent form for legal guardian or person responsible

Information/consent form for legal guardian or person responsible

Evidence of support / permission of elders and/or other appropriate bodies

Participant information elements

Core Elements

Provision of information to participants about the following topics should be considered for all research projects.
### About the project
- Full title and / or short title of the project
- Plain language description of the project
- Purpose / aim of the project and research methods as appropriate
- Demands, risks, inconveniences, discomforts of participation in the project
- Outcomes and benefits of the project
- Project start, finish, duration

### About the investigators / organisation
- Researchers conducting the project (including whether student researchers are involved)
- Organisations which are involved / responsible
- Organisations which have given approvals
- Relationship between researchers and participants and organisations

### Participant description
- How and why participants are chosen
- How participants are recruited
- How many participants are to be recruited

### Participant experience
- What will happen to the participant, what will they have to do, what will they experience?
- Benefits to individual, community, and contribution to knowledge
- Risks to individual, community
- Consequences of participation

### Participant options
- Alternatives to participation
- Whether participation may be for part of project or only for whole of project
- Whether any of the following will be provided: counselling, post research follow-up, or post research access to services, equipment or goods

### Participants rights and responsibilities
- That participation is voluntary
- That participants can withdraw, how to withdraw and what consequences may follow
- Expectations on participants, consequences of non-compliance with the protocol
- How to seek more information
- How to raise a concern or make a complaint

### Handling of information
- How information will be accessed, collected, used, stored, and to whom data will be disclosed
- Can participants withdraw their information, how, when
- Confidentiality of information
- Ownership of information
- Subsequent use of information
- Storage and disposal of information

### Unlawful conduct
- Whether researcher has any obligations to report unlawful conduct of participant

### Financial issues
- How the project is funded
- Declaration of any duality of interests
- Compensation entitlements
- Costs to participants
- Payments, reimbursements to participants
- Commercial application of results

### Results
- What will participants be told, when and by whom
- Will individual results be provided
- What are the consequences of being told or not being told the results of research
- How will results be reported / published
- Ownership of intellectual property and commercial benefits

### Cessation
- Circumstances under which the participation of an individual might
Describe what steps, if any, will be taken to ensure that the relationship does not impair participants' free and identified data.

Sydney Melanoma Diagnostic Centre

No

'standard care' will be taken from high risk individuals in the project.

45

Provide the start and finish dates for the whole of the study including data analysis.

Sponsor

Is this a study where capitation payments are to be made, and will participants be made aware of these payments to the research project?

Online Forms

Within which Jurisdictions will your research application be submitted to:

4.

Answers to the questions in section 8.1 will establish whether an HREC will need to apply guidelines under federal or state legislation.

16.

Tick as many of the following 'types of research participants' who will be included because of the project design, or if they areidentifiable.

3.

3.

Annual reports will be provided to Sydney Catalyst as required through receipt of the scholar award.

Australia. Evidence of the costs per melanoma excised, and numbers of excisions per melanoma detected, have been published.16

Community

quality adjusted life year) allowing comparison of cost effectiveness to be made with other government funded health interventions.

16

Evidence of the costs per melanoma excised, and numbers of excisions per melanoma detected, have been published.16

Top

Professor Graham Mann

peoples

No

No

Researchers will not be able to identify participants once linkage has been completed. Once linkage has been completed, identifiers are removed from the dataset and also the Medicare Australia Data. MBS data will be accessed according to the terms of the researcher. Only those identifiers necessary to the research will be merged with de-identified data set by CHeRel. Data will have an identifying Project Person Number (PPN) or a unique identifier. Use and disposal of personally identifiable data with the process conducted at secure facilities by the researcher and the University. Any possible breach of confidentiality will be reported to the Ethics Committee and/or the Data Governance Committee.

Specific to project or participant group

Aboriginal and/or Torres Strait Islander peoples

Additional issues to consider in participant information

Describe consultation process to date and involvement of leaderswhether ATSI status will be recorded.

Research Specific Elements

Provision of information to participants about the following topics should be considered as may be relevant to the research project.

Specific to project or participant group

Aboriginal and/or Torres Strait Islander peoples

Additional issues to consider in participant information

Describe consultation process to date and involvement of leaderswhether ATSI status will be recorded.

Circumstances under which the project might be terminated

cease

No
The cost-effectiveness of managing individuals at high risk of melanoma in a High Risk Clinic, compared with standard care.

Version 5, September 2013

Principal Investigator

Dr Anne Cust (primary PhD supervisor)
Senior Research Fellow, Cancer Epidemiology and Services Research (CESR), School of Public Health, University of Sydney,

Co-Investigators
Ms Caroline Watts
PhD student, Cancer Epidemiology and Services Research (CESR), School of Public Health, University of Sydney

Dr Rachael Morton
Research Fellow, School of Public Health, University of Sydney

Professor Graham Mann
Deputy Director, Westmead Institute for Cancer Research, Westmead Millennium Institute and Melanoma Institute Australia

Professor Scott Menzies
Director, The Sydney Melanoma Diagnostic Centre, Sydney Cancer Centre, Royal Prince Alfred Hospital,

Associate Researchers
Dr Timothy Dobbins
Senior Lecturer, Cancer Epidemiology and Services Research (CESR), School of Public Health, University of Sydney

Mr Chris Goumas
Data Analyst, Cancer Epidemiology and Services Research (CESR), School of Public Health, University of Sydney

 Protocol Version 5, September 2013
**Synopsis**

Melanoma is the third most common cancer in NSW. Some individuals are at higher risk than the general population because of genetic predisposition, family history, previous melanoma, many naevi (moles) or other factors. Early detection is a primary factor in survival and the rationale for screening individuals at high risk of melanoma. The aim of this study is to determine if it is cost effective from the perspective of the Australian health system to manage individuals considered at high risk of melanoma in a specialised setting, i.e. a high risk clinic, compared with standard care. The study is a modeled economic evaluation utilising mostly retrospective data relating to health costs and outcomes associated with a diagnosis of melanoma from high risk individuals managed either in a high risk clinic (intervention group) or in the community (standard care). The intervention group will be modeled on data from individuals attending the high risk clinic at Royal Prince Alfred hospital. Information from the comparator group will be obtained from high risk individuals selected from the Melanoma Patterns of Care study and the 45 and Up study. The 45 and Up study data will be linked through the Centre for Health Record Linkage (CHeReL) with the Central Cancer Registry and Admitted Patient Data Collection and through the Sax Institute with the Medicare Benefits Schedule. This research will provide evidence to allow the evaluation of both costs and benefits of the high-risk clinic model from an economic perspective, and will have direct policy implications for the management of individuals at high risk of melanoma in Australia.

**Background**

Cutaneous melanoma is the fourth most common cancer in both men and women in Australia¹ and the third most common cancer in NSW.² From 2002-2007 the incidence of melanoma in Australia steadily increased, and this trend is expected to continue.³ It has been long recognized that certain groups in the population have a greater chance of developing melanoma than the general population.³,⁴ Some factors that place individuals at high risk for developing melanoma include familial predisposition,⁵ a previous personal history of melanoma,⁶ and the presence of clinically dysplastic nevi (i.e. moles)⁷ or many melanocytic nevi,⁸ which may be classified as dysplastic nevus syndrome (DNS), familial melanoma in the presence of DNS, atypical moles (FAMMM syndrome) or atypical mole syndrome (AMS).⁹

Population screening is currently not recommended in Australia.¹⁰ Recommendations are for General Practitioners are to assess their patient’s risk of melanoma and develop surveillance programs accordingly.¹⁰ Early detection is a primary factor in survival and the rationale for screening individuals at high, risk.¹¹,¹² Opportunistic screening or targeting high risk groups for screening have been shown to be effective in diagnosing melanomas earlier than in non surveillance groups.¹³,¹⁴ Studies have shown regular surveillance of high risk groups assists with early detection.¹³,¹⁵,¹⁶ A Queensland study has shown that diagnostic pathways for managing individuals with melanoma are quite diverse.¹⁷

A High Risk Clinic (HRC) was established in 2006 at the Royal Prince Alfred Hospital, Sydney, with the aim of improving the management of individuals at high risk of melanoma. Three additional HRCs...
are also being set up in NSW based on this model. In this study, we will conduct a modeled economic evaluation using mostly retrospective data and linked data from various sources to determine if it is cost effective from the perspective of the Australian health system to manage individuals considered at high risk of melanoma in a specialised setting, i.e. a high risk clinic, compared with standard care. This research will provide evidence to allow the evaluation of the high-risk clinic model from an economic perspective. This information will have direct policy implications for the management of individuals at high risk of melanoma in Australia.

**Aims and significance**

The aim of this study is to determine if it is cost-effective to manage individuals considered at high risk of melanoma in a specialised setting, i.e. a High Risk Clinic, compared with standard care. This study has direct relevance to health policy in NSW as a potential model of clinical management that is currently being evaluated and expanded to several locations in NSW in 2012.

**Objectives**

**Primary objective**
- From the perspective of the Australian health care system, to calculate the incremental costs and incremental benefits of managing patients at high risk of melanoma in NSW within a specialized High Risk Clinic compared with standard care.

**Secondary objectives**
- From a societal perspective, to calculate the incremental costs and incremental benefits of managing patients at high risk of melanoma in NSW within a specialized High Risk Clinic compared with standard care.
- To determine if the cost-effectiveness of the High Risk Clinic applies equally to particular subgroups at high risk of melanoma
- To determine which parameters are most sensitive to change and their effect on the incremental cost effectiveness ratio (ICER). For example, numbers attending the clinics, health system costs, surveillance costs.
- To determine if it is more cost-effective to situate High Risk Clinics in areas of NSW with the highest incidence of melanoma (such as the North Coast Health Area).

**Methods**

**Study design**

The study is a modeled economic evaluation utilizing mostly retrospective data and linked data from various sources relating to health costs and outcomes associated with a diagnosis of melanoma from high risk individuals managed either at a High Risk clinic (intervention group) or in standard care.

Protocol Version 5, September 2013
**Study population**

Costs and benefits for the intervention group will be modeled on data from individuals attending the High Risk Clinic at the Royal Prince Alfred Hospital since 2006. ‘High risk’ for the purposes of this study is defined as individuals over 18 years with a familial or genetic predisposition to melanoma, or a history of a previous melanoma.

Specifically, the definition includes individuals with either:

1. Dysplastic naevus syndrome (defined as >100 naevi or ≥1 naevus 8mm diameter or >5 dysplastic naevi) and at least one previous primary invasive melanoma
2. Personal history of 2 or more primary invasive melanoma, with at least 1 melanoma within the last 10 years
3. A known mutation in the high penetrance CDKN2A or CDK4 genes
4. A strong family history of melanoma defined as 4 or more first or second degree relatives with melanoma including oneself.

The comparator is the standard care population, who are not managed in the High Risk Clinic, and are derived from a population of high risk individuals selected from the Melanoma Patterns of Care Study (MPOC) and The 45 and Up cohort study, both conducted in NSW. All individuals in the MPOC study have a confirmed melanoma. In addition, to be classified as ‘high risk’ for the purpose of our study, a treating clinician had to report that the patient had either:

1. A previous melanoma
2. Lots of moles
3. A family history of melanoma in a blood relative

We define ‘high risk’ in The 45 and Up Study as:

1. A individual with a self-report of melanoma (confirmed by the Central Cancer Registry) and a report of melanoma in 2 blood relatives

**Data sources**

**Intervention group**

The High Risk Clinic (HRC) was established in 2006 at the Royal Prince Alfred Hospital, Sydney, with the aim of improving the management of individuals at high risk of melanoma. Participants in the clinic are screened at 6 monthly intervals using a variety of clinical imaging techniques, dermoscopy, digital monitoring and total body photography. Individuals are managed according to the assessment of any lesions detected. If a suspicious lesion is detected the surveillance interval may be decreased for closer surveillance or the lesion excised. All monitoring and treatment is documented to ensure efficient continuity of care. Education in self screening techniques is provided and a record of self screening is also maintained. Approximately 300 individuals are currently enrolled in the High Risk Clinic program at this hospital. Permission for use of potentially re-identifiable data from this study has been given by the chief investigator of the High Risk Clinic, subject to ethics approval.

Professor Scott Menzies has submitted an amendment under his Protocol No X11-0409 and HREC/11/RPAH/636 to RPAH ethics committee for Caroline Watts to observe the High Risk Clinic and
document service provision. To cost the service provision, we will assign costs related to the procedures performed from the MBS schedule (www.mbsonline.gov.au/).

**Standard care group**

Standard care involves intermittent surveillance of the skin without the use of digital monitoring or total body photography. The information about treatment and management of individuals diagnosed with melanoma for the standard care model will be taken from the Melanoma Patterns of Care (MPOC) study and The 45 and Up study.

An initiative of The Melanoma Network, the MPOC study details the medical management of 2708 individuals diagnosed in NSW with a melanoma confirmed by the NSW Cancer Registry between October 2006 and October 2007. Information about how the melanoma was identified, management and treatment history and follow-up recommendations can be obtained from this report. Permission has been given from the chief investigators to use a de-identified MPOC data set containing patterns of care information relating to high risk individuals, for use in this proposed study.

The 45 and Up study, is a long term cohort health study of the health of 123,779 men and 143,069 women over 45 years of age who live in NSW. We would expect that about 700 individuals will be considered ‘high risk’, based on an estimate that 5% of 14,596 participants who reported they had been diagnosed with melanoma will have two first degree relatives with melanoma, as measured on the 45 and Up study questionnaire. Identification of individuals in the 45 and Up Study who are also in the High Risk Clinic program will be managed in the following way: Any 45 and Up study participant who has an MBS item for a frequently occurring consultation at the scheduled fee, on known dates of service (the clinic runs on the same two days every week) and that corresponds with the provider postcode, will be removed from the standard care data set.

The 45 and Up study is managed through the Sax Institute and they also maintain the linked data from Medicare Australia. Through linked data access to Medicare Australia, we will obtain information about excisions, treatment costs, out of pocket costs, and distance to treatment centre. Data from the 45 and Up study will also be linked with data from the NSW Central Cancer Registry (CCR) via CHeReL (Centre for Health Record Linkage) to confirm the self report of melanoma. All reports of melanoma, including multiple invasive and in situ reports of melanoma will be requested from the Cancer Registry. Where a report of melanoma is confirmed, we will record important clinical and histopathological details provided by the Cancer Registry such as Breslow thickness. CHeReL will also oversee linkage with the Admitted Patient Data Set (APDS) so that health resource usage and cost associated with treatment can be estimated. From the MBS data in The 45 and Up Study, we will track the procedures related to the date of the melanoma excision, as well as other excisions within the period of interest.

**Prospective data**

In order to obtain information about health-related quality of life and other items relevant to our cost-effectiveness analysis, we intend to administer a questionnaire to approximately 60 individuals who are being managed in the HRC and another group of high risk individuals who are receiving

Protocol Version 5, September 2013
standard care (i.e. are not attending the HRC). Ethics approval for this additional data collection will be sought in 2013.

Expected duration of study and start times

Ethics application submitted June 2012.
Following ethics approval, linked data sets will be available for analysis by April 2013. It is expected that the data analysis and economic modeling will be completed by the end of 2013 and the thesis submitted by July 2014.

Linkage process

The 45 and Up study population will be linked via CHeReL using the Master Linkage key to NSW Central Cancer Registry to confirm all reports of melanoma. The Master Linkage key will be used to link individuals with confirmed reports to the Admitted Hospital Patient Dataset. Data linkage will also occur at the Sax Institute in accordance with The 45 and Up Study governance requirements for use of the Medicare Benefits Scheme dataset.

Flowchart of data linkage process
Health outcomes

Health outcomes for the cost-effectiveness analysis will include the number of excisions, the number of melanomas detected, Breslow depth, patient survival measured in years, and the patient quality-adjusted survival measured in quality-adjusted life years (QALYs). QALY weights will be taken from the literature for patients with the above mentioned health states, and also collected prospectively using the FACT-M and/or EQ-5D instruments as an amendment to the study in 2013. This questionnaire will also include an out of pocket patient costs questionnaire referred to below in statistical methods.

Primary and secondary outcomes

Primary outcomes
The primary outcome is the incremental cost effectiveness ratio (ICER) of costs incurred by the health system in the management of individuals at high risk of melanoma in NSW and benefits to the patient based on a modeled comparison of individuals managed through a ‘High Risk Clinic’ surveillance model and those who experience standard care in NSW.

Total costs at 20 years and total benefits or health outcomes at 20 years will be presented. Incremental cost effectiveness ratios for AUD ($) per excision avoided and AUD ($) per melanoma detected will be calculated. Results will be also presented as incremental cost effectiveness ratio of AUD ($) per life year saved and AUD ($) per quality adjusted life year.

The results will presented as treatment costs and health outcomes based on:
- Breslow depth at diagnosis of new melanoma
- number of excisions
- quality of life outcomes (based on utilities)
- expected morbidity
- expected survival

Secondary outcomes
We will collect information about costs incurred from a societal perspective in the management of individuals at high risk of melanoma in NSW. In addition to the above outcomes we will investigate the impact of; patient out of pocket expenses, time off work, productivity losses, distance from home to the treatment centre and socio-economic demographic factors on the cost effectiveness of the high risk clinic.

Statistical Methods

To determine cost effectiveness, a Markov Model (Treeage Pro 2011 Williamstown USA) will be built. This model is designed to simulate the long term outcomes based on the natural history of a disease. The model will comprise a number of health states; including no melanoma, Stage I, Stage II melanoma, recurrent melanoma, and deaths from all causes. The model is populated with the probabilities of transition through the health states over a twenty year time period. The model will contain quality-adjusted life year (QALY) measures or utility values for the different health states and...
their associated costs for surveillance and treatment. The model will run for 20 annual cycles to calculate disease progression and the costs and benefits of treatment over the twenty year time horizon.

The MPOC study will be used to define the characteristics of the high risk population in NSW. For analysis, some high risk groups will have one risk factor and other groups will contain more than one risk factor, for example family history and many moles. The MPOC data will be used to determine the numbers in each risk group. The frequencies of characteristics of this high risk cohort will be extrapolated, in terms of the expected costs and health effects, for 1000 individuals to model standard care compared to a ‘High Risk Clinic’ pattern of care.

The patterns of care of individuals at high risk of melanoma, including patterns of surveillance and treatment will be assessed over 12 months for the standard care group and the high risk clinic group. These data will provide information about treatment pathways and outcomes that will be used in the model. For the standard care group the MPOC data will be supplemented by linkage data from individuals with confirmed melanomas linked to the MBS dataset through the 45 and Up study and through the CHeReL also linked via the Master Linkage Key to the CCR and APDC to examine both health outcomes and resource use. Public hospital costing data will be calculated using National Hospital Cost Data Collection (NHCDC) using average cost per diagnosis related group (DRG) and length of stay. Procedure codes and diagnosis codes for the patients’ admissions will be used to select patients admitted for melanoma related treatment. The NHCDC was selected as both private and public hospitals are included in deriving an estimation of costs and it is more suitable for patient level costing. Medical costs for surveillance and follow up will be calculated according to the current 2011 Medicare Benefits Schedule and are based on category of clinician, treatment provided and size and type of lesion excised. Other costs such as equipment and overheads will be derived from current market estimations. Costs and outcomes in the future will be discounted by 5%, the standard rate recommended by the Australian Pharmaceutical Benefits Advisory Committee.

Measures for survival will be based on the American Joint Cancer Committee staging criteria 2009. To estimate societal costs, Medicare Benefits Schedule service records linked to the 45 and Up study will be used to examine out of pocket costs and travel distance to medical care, employment status, socio- economic status. It is envisaged that further prospective data collection will be required to further examine patient out of pocket cost and lost work time and approval for this will be requested in 2013 as an amendment for this study.

We will use SAS statistical analysis software (SAS Institute Inc) and Treeage software to create the cost effectiveness models.

**Sensitivity and subgroup analysis**

We will examine the robustness of our results by conducting the following sensitivity and subgroup analyses:

1. Variations in the number of people considered at high risk for melanoma will be examined and assessed for impact on cost effectiveness

Protocol Version 5, September 2013
2. The frequency of follow-up and the effect of increasing or decreasing screening intervals for the high risk group in both the high risk clinic and in standard care.
3. Modifying the assumptions about numbers of lesions biopsied per melanoma detected.
4. Sensitivity and specificity of various screening techniques; i.e. dermoscopy, confocal microscopy
5. Cost effectiveness for subgroups at high risk; i.e. those with family history, those with dysplastic naevus syndrome, those with a previous melanoma or known mutation

**Ethical considerations**

**Data from the Melanoma Patterns of Care (MPOC) study**

We requested a waiver of consent for this project for the use of potentially re-identifiable data from the MPOC study. The aim of the MPOC study was to assess the quality of medical care for patients with a newly diagnosed melanoma in NSW and to improve cancer control. We believe our study, which aims to contribute to discussion about how to best to manage individuals at high risk of melanoma in NSW, is aligned with these values.

Individual patient consent was not obtained for the MPOC study for a number of reasons: firstly, participants would expect their information at the Central Cancer Registry to be used for research that could improve cancer control; secondly, it was important to have a data set that accurately reflected the management of melanoma in NSW to ensure study goals were met, which would require high participation; and lastly, it was also considered that contacting individuals within a short time of their diagnosis could cause distress. To obtain data for the MPOC project, medical practitioners were contacted and asked to fill in a questionnaire, which, if completed, was taken as indicating implied consent for provision of the information. The data held outside the Cancer Registry, which will be used for this cost-effectiveness project, have been de-identified. The MPOC investigators have agreed to provide data relating to high risk individuals for this project and are supportive of our project.

**Data from the High Risk Clinic (HRC)**

The High Risk Clinic is a clinical research project that is examining both melanoma detection methods and effectiveness of surveillance of individuals at high risk of melanoma in a specialized clinic setting. This program at the Sydney Melanoma Diagnostic centre is funded by a CINSW Translational Research Grant. This project commenced in 2006 and expanded to another three sites in 2012.

We requested a waiver of consent for this project for the use of potentially re-identifiable data from the HRC study. All participants were asked to read an information sheet prior to providing consent to participate in research at the HRC. The consent form states that researchers associated with the
larger Translational Research Grant will have access to the data from this research. Our project is integral in evaluating the effectiveness of the HRC and Professor Scott Menzies, Director of the Sydney Melanoma Diagnostic Centre, is supportive co-investigator on this project. The data custodians have provided their approval for use of the HRC datasets. Potentially re-identifiable data from the 2006-2010 HRCs will be used for the outcomes and treatment costs of specialized care. The data will be obtained from a third party, with identifying information removed.

**Analysis of the linked data sets using the SURE facility**

*The SURE facility and security controls*

The SURE (Secure Unified Research Environment) is a remote access computing environment which is accessible over encrypted AARNet connection. The SURE curated gateway is a specialized application that has been developed to allow the transfer of files securely in and out of the SURE facility. All data transferred is protected via SSL encryption, and will be accessed primarily at the University of Sydney. SURE website: [https://www.saxinstitute.org.au/our-work/sure/](https://www.saxinstitute.org.au/our-work/sure/) To log on to SURE, a user needs authentication credentials that are assigned by the SURE team. These credentials are:

- A username
- A passphrase
- A physical token called a Yubikey supplying a one-time passcode
- A digital client certificate installed on the local computer used to access SURE

To transfer data via the SURE curated gateway the user must access SURE. Data files are stored centrally on servers housed in a secure data centre. Data are analysed within SURE and there are strong security controls to protect the confidentiality of the data files. Files cannot be printed or copied. Files moving in and out of SURE are monitored by the chief investigator, logged by SURE and may be audited by the SURE team. This is to ensure compliance with ethics committee approval and data custodian requirements. After the research is completed, files will be stored by the SURE facility in an encrypted format for seven years.

**Analysis of our linked dataset in SURE**

Data analysis of the MBS data and 45 and Up study data will be through the SURE in accordance with the governance requirements of the 45 and Up Study. It is only possible to access the 45 and Up linked dataset through the SURE facility, thus in order to analyse our fully linked dataset, it is necessary to also move the linked APDC dataset and CCR dataset to the SURE facility. Thus, the APDC dataset and CCR dataset will be analysed both on secure servers at the University of Sydney and also within the SURE. The researchers Dr Anne Cust and Ms Caroline Watts have completed the full-day SURE user training program that ensure users are aware of the data security and legislative and ethical requirements as well as covering issues regarding accessing and using the SURE facility.

**Data transfer from The University of Sydney server to SURE, and security of information**

The APDC and CCR datasets will be uploaded to the SURE facility by the Investigators (Dr Anne Cust and Caroline Watts) as required, and the 45 and Up dataset will be uploaded by the SAX Institute. At the end of the study, the CCR data and APDC data will be moved out of the SURE and stored on the University of Sydney secure servers.

Protocol Version 5, September 2013
Security of linked data at The University of Sydney
Data not held within SURE will be stored securely on the researcher’s password protected computer (on the University server) in Room 202, Queen Elizabeth Research Building, University of Sydney. These data will be backed up daily on a server managed by the Information and Communications Department at the University of Sydney. Access to this drive is login and password protected. A backup copy of the dataset will be stored on a DVD that will be kept in a locked filing cabinet within the locked offices of the Cancer Epidemiology and Services Research Group. Access to the building where the database is stored requires a passcard. The office is locked in the evening. In late 2013 or early 2014, our research group (Cancer Epidemiology and Services Research) will be moving to the Chris O’Brien Lifehouse, on level 6, which will be University of Sydney premises. Our office space will be in a secure area requiring a passcard, and we will have locked filing cabinets and the same secure University IT systems in place. The data will be held on the server for 7 years after completion of the project. The file will be removed after this time.

Presentation of data
The risk to privacy of patients if their information is re-identified is that their predisposition to melanoma and their subsequent melanoma care may become known, however the probability of re-identification of patients is extremely small as all data are de-identified prior to being provided to the researcher for analysis. Additionally, all de-identified data will be aggregated into an average of costs and benefits before presentation or publication. Small subsets of data will not be presented or published.

Multiple reports of in situ and invasive melanomas
We will abide by the data custodian’s conditions of release of the data, which include that we are not to report rates of in situ melanoma, and that we should take care when interpreting the data from multiple invasive cancers. We will ensure that all the researchers on this project are aware of these conditions and any reporting of the data will be checked by multiple members of the study team before any publication or presentation.

Outcomes and significance
This research will provide evidence to allow the evaluation of both costs and benefits of the high-risk clinic model and will have direct policy implications for the management of individuals at high risk of melanoma in Australia. Results will be presented using standard outcomes (i.e. cost per life year saved and cost per quality adjusted life year), allowing comparisons of cost effectiveness to be made with other government funded health interventions.

Publication Policy
Publications will be in accordance with the University of Sydney Research Agreement Policy 2011. The 45 and Up study publication policy as per the data use agreement will also be followed.

Protocol Version 5, September 2013
References

1. AIHW. Cancer in Australia 2010: an overview. Cancer Series no 60 2010;Cat. no. CAN 56. (Canberra: AIHW).


18. Melanoma Network. Melanoma Patterns of Care Study.
29 August 2012

Professor S Menzies
C/- Dr E Coates
Sydney Melanoma Diagnostic Centre
Level 3, Building 88
Royal Prince Alfred Hospital

Dear Professor Menzies,

Re: Protocol No X11-0409 & HREC/11/RPAH/636 - “A multicentre observation of a cohort who are at high risk for the development of primary melanoma of the skin”

The Executive of the Ethics Review Committee, at its meeting of 31 May 2012, considered your correspondence of 24 May 2012, concerning amendments to the above study, as part of an associated study to assess the cost effectiveness of the High Risk Clinic compared with standard care being reviewed by the NSW Population and Health Services Research Ethics Committee:

- Observation of the high risk clinic by a research assistant, Ms Caroline Watts, under your supervision;

- Medical records review of relevant patients of the High Risk Clinic

The inclusion of Ms C Watts as a research assistant in the above study was noted and approved.

The Committee would be pleased to receive a copy of the ethics approval letter for the study from the NSW Population and Health Services Research Ethics Committee, and a copy of the Data Collection Form that will be used to extract study data from medical records, in due course.

[Signature]
You are advised that Ms Watts' role in the study will also require governance authorisation for the RPAH site before she is given access to the clinic and the medical records. In addition, she may require a criminal record check and to arrange this she should contact Ms Maree Larkin on 9515 7899 (after 25 September 2012).

I apologise for the delay in responding to this correspondence.

Yours sincerely,

Lesley Townsend
Executive Officer
Ethics Review Committee (RPAH Zone)

HERC\EXECOR\12-06
Ms Caroline Watts  
School of Public Health  
Sydney Medical School  
QE II Research Bldg D02  
University of Sydney NSW 2006  

11 April 2013  

Dear Ms Watts,  

NSW Population & Health Services Research Ethics Committee  

AU RED Reference: HREC/12/CIPHS/57  

Cancer Institute NSW reference number: 2012/07/409  

Project Title: The cost effectiveness of managing individuals at high risk of melanoma in a High Risk Clinic, compared with standard care  

Thank you for your recent correspondence notifying of changes to the above referenced study, submitted for single ethical review to the NSW Population & Health Services Research Ethics Committee (Executive). The Committee reviewed your amendments at its meeting held on 8 April 2013, and I am pleased to advise that ongoing ethical approval has been granted.

The Committee approved the following documentation:  
- Cover Letter, dated 13 March 2013  
- CI NSW Request for Amendment form, dated 13 March 2013  
- Protocol, Version 2, dated March 2013  

The NSW Population & Health Services Research Ethics Committee has been accredited by the NSW Department of Health to provide single ethical and scientific review of research proposals conducted within the NSW public health system.

The Committee is a joint initiative of the Cancer Institute NSW and NSW Department of Health. The Committee has been constituted and operates in accordance with the National Health and Medical Research Council’s National Statement on Ethical Conduct in Human Research (2007) and relevant legislation and guidelines.

You are reminded that this letter constitutes ‘ethical approval’ only. This research project must not commence at a site until separate authorisation from the Chief Executive or delegate of that site has been obtained. It is your responsibility to forward a copy of this letter together with any approved documents as enumerated above, to all site investigators for
submission to the site’s Research Governance Officer. Where relevant, copies will also need to be provided to the CHeReL and the data custodian. For further information about the NSW Population & Health Services Research Ethics Committee, please refer to our website www.cancerinstitute.org.au/research.

Should you have any queries about the ethical review of your research proposal, please contact me on 02 8374 3562 or email ethics@cancerinstitute.org.au.

The NSW Population & Health Services Research Ethics Committee wishes you well in your research endeavours.

Yours sincerely,

Virginia Turner
Ethics Coordinator
Cancer Institute NSW
Dr Anne Cust  
Senior Research Fellow  
Cancer Epidemiology and Services Research  
Sydney School of Public Health  
University of Sydney  
NSW 2006

24 July 2013

Dear Dr Cust,

NSW Population & Health Services Research Ethics Committee

AU RED Reference: HREC/12/CIPHS/57

Cancer Institute NSW reference number: 2012/07/409

Project Title: The cost effectiveness of managing individuals at high risk of melanoma in a High Risk Clinic, compared with standard care.

Thank you for your correspondence of 12 July 2013 notifying of changes to the above referenced study, submitted for single ethical review to the NSW Population & Health Services Research Ethics Committee. The Executive Committee reviewed your amendment on 22 July 2013, and I am pleased to advise that ongoing ethical approval has been granted.

The Committee approved the following documentation:

- CI NSW Request for Amendment form, dated 12 July 2013 (to access multiple episodes of invasive melanoma as reported to the Cancer Registry)
- Data custodian sign-off form dated 8/07/2013
- Protocol Version 3, July 2013

The NSW Population & Health Services Research Ethics Committee has been accredited by the NSW Ministry of Health to provide single ethical and scientific review of research proposals conducted within the NSW public health system.

The Committee is a joint initiative of the Cancer Institute NSW and NSW Department of Health. The Committee has been constituted and operates in accordance with the National Health and Medical Research Council’s National Statement on Ethical Conduct in Human Research (2007) and relevant legislation and guidelines.

You are reminded that this letter constitutes ‘ethical approval’ only. This research project must not commence at a site until separate authorisation from the Chief Executive or delegate of that site has been obtained. It is your responsibility to forward a copy of this letter...
together with any approved documents as enumerated above, to all site investigators for submission to the site’s Research Governance Officer. Where relevant, copies will also need to be provided to the CHeReL and the data custodian.

For further information about the NSW Population & Health Services Research Ethics Committee, please refer to our website [www.cancerinstitute.org.au/research](http://www.cancerinstitute.org.au/research).

Should you have any queries about the ethical review of your research proposal, please contact me on 02 8374 3562 or email ethics@cancerinstitute.org.au.

The NSW Population & Health Services Research Ethics Committee wishes you well in your research endeavours.

Yours sincerely,

[Signature]

Virginia Turner  
Ethics Coordinator  
Cancer Institute NSW
Dr Anne Cust  
Senior Research Fellow  
Cancer Epidemiology and Services Research  
Sydney Shool of Public Health  
University of Sydney  
NSW 2006

26 September 2013

Dear Dr Cust,

NSW Population & Health Services Research Ethics Committee

AU RED Reference: HREC/12/CIPH/57

Cancer Institute NSW reference number: 2012/07/409

Project Title: The cost effectiveness of managing individuals at high risk of melanoma in a High Risk Clinic, compared with standard care.

Thank you for your recent correspondence notifying of changes to the above referenced study, submitted for single ethical review to the NSW Population & Health Services Research Ethics Committee (Executive). The Committee reviewed your amendments at its meeting held on 25 September 2013, and I am pleased to advise that ongoing ethical approval has been granted.

The Committee approved the following documentation:

- Cover letter, dated 4 September 2013
- CI NSW Request for Amendment form, dated 4 September 2013
  o Amendment requesting to move CCR & APDC Data to the online secure SURE facility.
- Protocol, Version 4, dated September 2013

The NSW Population & Health Services Research Ethics Committee has been accredited by the NSW Ministry of Health to provide single ethical and scientific review of research proposals conducted within the NSW public health system.

The Committee is a joint initiative of the Cancer Institute NSW and NSW Department of Health. The Committee has been constituted and operates in accordance with the National Health and Medical Research Council’s National Statement on Ethical Conduct in Human Research (2007) and relevant legislation and guidelines.

You are reminded that this letter constitutes ‘ethical approval’ only. This research project must not commence at a site until separate authorisation from the Chief Executive or
delegate of that site has been obtained. It is your responsibility to forward a copy of this letter together with any approved documents as enumerated above, to all site investigators for submission to the site’s Research Governance Officer. Where relevant, copies will also need to be provided to the CHeReL and the data custodian.

For further information about the NSW Population & Health Services Research Ethics Committee, please refer to our website www.cancerinstitute.org.au/research.

Should you have any queries about the ethical review of your research proposal, please contact me on 02 8374 5615 or email ethics@cancerinstitute.org.au.

The NSW Population & Health Services Research Ethics Committee wishes you well in your research endeavours.

Yours sincerely,

Samantha Dawes
Administration Support Officer
Cancer Institute NSW
Ms Caroline Watts  
School of Public Health  
Sydney Medical School  
QE II Research Bldg D02  
University of Sydney NSW 2006

12 October 2012

Dear Ms Watts,

**NSW Population & Health Services Research Ethics Committee**

**AU RED Reference: HREC/12/CIPHS/57**

**Cancer Institute NSW reference number: 2012/07/409**

**Project Title: The cost effectiveness of managing individuals at high risk of melanoma in a High Risk Clinic, compared with standard care**

Thank you for your correspondence responding to a request for further information/clarification of the above referenced study, submitted to the NSW Population & Health Services Research Ethics Committee (Executive) for single ethical and scientific review. The Committee reviewed your response at its meeting held on 2 October 2012 and I am pleased to inform you that full ethical approval has been granted.

The Committee approved the following documents:

- NSW National Ethics Application Form, v2, submission code AU/1/FD7D013, dated 25 May 2012
- Research Protocol, Version 1, dated June 2012
- CHeReL Application for Data
- 2012.15 – CHeReL linkage plan
- NSW CCR – Variable checklist
- APDC Variable checklist
- 45 and Up Study – Variable checklist
- External dataset (s) – Variable list
- CHeReL Letter of Feasibility, dated 28 May 2012
- Data Custodian sign off (with caveats), NSW CCR, dated 7 June 2012
- Data Custodian sign off, APDC, dated 29 June 2012
- Data Custodian sign off, 45 and Up Study, dated 28 June 2012
- Researcher response letter, dated 14 August 2012
- Researcher response letter, dated 4 September 2012
- Approval letter from NSW PHSREC for Melanoma Patterns of Care (Sub-Study 1) - Survey of patterns of care for patients with newly diagnosed melanoma, dated 29 August 2006
• Approval letter from SSWAHS Ethics Review Committee for Observation of a high risk clinic for primary melanoma, dated 20 December 2005
• Researcher response letter, dated 25 September 2012
• NSW Privacy Form (submitted 25 September 2012)

Approval is now valid for the following sites:
• Sax Institute
• University of Sydney

The NSW Population & Health Services Research Ethics Committee (Executive) has been accredited by the NSW Department of Health to provide single ethical and scientific review of research proposals conducted within the NSW public health system.

The Committee is a joint initiative of the Cancer Institute NSW and NSW Department of Health. The Committee has been constituted and operates in accordance with the National Health and Medical Research Council’s National Statement on Ethical Conduct in Human Research (2007) and relevant legislation and guidelines.

Please note that ethical approval is valid for 5 years, conditional on the following:

• Principal investigators will immediately report anything which might warrant a review of ethical approval of the research, including unforeseen events that might affect continued ethical acceptability.
• Proposed amendments to the research proposal or conduct of the research which may affect the ethical acceptability of the research are to be provided to the NSW Population & Health Services Research Ethics Committee for review.
• The NSW Population & Health Services Research Ethics Committee will be notified giving reasons, if the research is discontinued before the expected date of completion.
• The Principal Investigator will provide an annual progress report to the NSW Population & Health Services Research Ethics Committee and at the completion of the study.

You are reminded that this letter constitutes ‘ethical approval’ only. This research project must not commence at a site until separate authorisation from the Chief Executive or delegate of that site has been obtained. It is your responsibility to forward a copy of this letter together with any approved documents as enumerated above, to all site investigators for submission to the site’s Research Governance Officer. Where relevant, copies will also need to be provided to the CHeReL and the data custodian.

For further information about the NSW Population & Health Services Research Ethics Committee, please refer to our website www.cancerinstitute.org.au/research.

Should you have any queries about the ethical review of your research proposal, please contact Kate Lowrie, Admin Support Officer – Ethics on 02 8374 5616 or email ethics@cancerinstitute.org.au.

The NSW Population & Health Services Research Ethics Committee wishes you well in your research endeavours.
The cost effectiveness of managing individuals at high risk of melanoma in a High Risk Clinic, compared with standard care

In situ melanoma cases are provided with the following caveats:

- Rates of in situ melanoma are not to be calculated. The numbers of in-situ melanomas are not to be reported or compared to the numbers of invasive melanomas. The reason for this is that the recording of invasive melanomas are subject to IARC coding rules to ensure comparability of trends over time while in situ melanomas are added to the database as they are reported and are mainly used for patient recruitment purposes.

Multiple invasive melanoma cases are provided with the following caveats:

- Multiple invasive cancer cases are not subject to the same quality assurance processes as the incident cases in the NSW Cancer Registries. Therefore, care should be taken when interpreting the data.
Dr Anne Cust  
Senior Research Fellow  
Cancer Epidemiology and Services Research  
Sydney School of Public Health  
University of Sydney  
NSW 2006

25 October 2013

Dear Dr Cust,

NSW Population & Health Services Research Ethics Committee

AU RED Reference: HREC/12/CIPHS/57

Cancer Institute NSW reference number: 2012/07/409

Project Title: The cost effectiveness of managing individuals at high risk of melanoma in a High Risk Clinic, compared with standard care.

Thank you for your recent correspondence notifying of changes to the above referenced study, submitted for single ethical review to the NSW Population & Health Services Research Ethics Committee (Executive). The Committee reviewed your amendments at its meeting held on 25 October 2013, and I am pleased to advise that ongoing ethical approval has been granted.

The Committee approved the following documentation:

- CI NSW Notification of Change in personnel form, dated 24 October 2013
  - Outgoing CPI Ms Caroline Watts, University of Sydney
  - Incoming CPI Dr Anne Cust, University of Sydney
- CV of Dr Anne Cust

The NSW Population & Health Services Research Ethics Committee has been accredited by the NSW Ministry of Health to provide single ethical and scientific review of research proposals conducted within the NSW public health system.

The Committee is a joint initiative of the Cancer Institute NSW and NSW Department of Health. The Committee has been constituted and operates in accordance with the National Health and Medical Research Council’s *National Statement on Ethical Conduct in Human Research (2007)* and relevant legislation and guidelines.
You are reminded that this letter constitutes 'ethical approval' only. This research project must not commence at a site until separate authorisation from the Chief Executive or delegate of that site has been obtained. It is your responsibility to forward a copy of this letter together with any approved documents as enumerated above, to all site investigators for submission to the site’s Research Governance Officer. Where relevant, copies will also need to be provided to the CHeReL and the data custodian.

For further information about the NSW Population & Health Services Research Ethics Committee, please refer to our website www.cancerinstitute.org.au/research.

Should you have any queries about the ethical review of your research proposal, please contact me on 02 8374 5615 or email ethics@cancerinstitute.org.au.

The NSW Population & Health Services Research Ethics Committee wishes you well in your research endeavours.

Yours sincerely,

Samantha Dawes
Administration Support Officer
Cancer Institute NSW
Yours sincerely,

A/Prof Sallie-Anne Pearson
Chairperson
NSW Population & Health Services Research Ethics Committee
## Appendix 9.4

### Summary of published utility scores for excision of melanoma, keratinocytic and benign lesions by stage at diagnosis.

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Country</th>
<th>Quality of life instrument</th>
<th>Patients with melanoma</th>
<th>Population description</th>
<th>Stage</th>
<th>Mean utility and scores (SD)(^1,2,4,5,6,7,8), (range)(^3)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tromme(^1) (2014)</td>
<td>Belgium</td>
<td>Euroqol EQ-5D-5L</td>
<td>395</td>
<td>First mth 0/IA Rx</td>
<td>0</td>
<td>0.687 (0.192)</td>
<td>157 in treatment and 238 in follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2-24(^{th}) mth 0/IA</td>
<td></td>
<td>0.809 (0.179)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>First 2 mths 1B/II Rx</td>
<td></td>
<td>0.579 (0.272)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3- 24(^{th}) mth 1B/II</td>
<td></td>
<td>0.802 (0.166)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>First 3 mths III Rx</td>
<td></td>
<td>0.535 (0.278)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt; 3 mths III</td>
<td></td>
<td>0.703 (0.156)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV Rx</td>
<td></td>
<td>0.583 (0.192)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV</td>
<td></td>
<td>0.796 (0.167)</td>
<td></td>
</tr>
<tr>
<td>Askew(^2) (2011)</td>
<td>USA</td>
<td>EQ-5D</td>
<td>273</td>
<td>Stage I/II(n=102) Stage III(n=100) and Stage IV(n=71) 75 in active Rx and 198 under surveillance. Med age 52 yrs.</td>
<td>Not given</td>
<td>0.91 (0.14)    0.91 (0.14) 0.85 (0.13) 0.86 (0.11)</td>
<td>Mapping from FACT-M to EQ-5D.</td>
</tr>
<tr>
<td>Wilson (2013)</td>
<td>UK</td>
<td>Time trade off</td>
<td>84</td>
<td>Based on the results from patients with a diagnosis of melanoma &gt;1 year Stage I (n=69), Stage II (n=8), Stage III (n=8)</td>
<td>0.93 (0.013)</td>
<td>0.93 (0.013)</td>
<td>0.87 (0.057)</td>
</tr>
<tr>
<td>King (2011)</td>
<td>USA</td>
<td>Time trade off</td>
<td>163</td>
<td>Stage I (n=95 (N 15, E 80)), Stage II (n=15 (N 4, E 11)), Stage III (n=18 (N 4, E 10)), Stage IV (n=35 (N 11, E 24))</td>
<td>NA</td>
<td>0.926 (0.119)</td>
<td>0.915 (0.127)</td>
</tr>
<tr>
<td>Hirst (2010)</td>
<td>Au</td>
<td>Standard gamble, Time trade off and expert opinion</td>
<td>Not stated</td>
<td></td>
<td>Dx 0</td>
<td>St 0</td>
<td>Dx STI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.95</td>
<td>1</td>
<td>0.937</td>
</tr>
<tr>
<td>Losina (2007)</td>
<td>USA</td>
<td>Time trade off</td>
<td>24</td>
<td>Based on the results from patients with a diagnosis of melanoma &lt;1 year Stage I (n=14), Stage II (n=3), Stage III (n=7)</td>
<td>0.937</td>
<td>0.937</td>
<td>0.52</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Method</td>
<td>Sample Size</td>
<td>Patient Description</td>
<td>Values</td>
<td>Disease free</td>
<td>No side effects</td>
</tr>
<tr>
<td>---------------</td>
<td>---------</td>
<td>-------------------</td>
<td>-------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>--------</td>
<td>--------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Beusterien⁶ (2009)</td>
<td>UK</td>
<td>Standard gamble</td>
<td>140</td>
<td>All patients with advanced metastatic melanoma. 77 from Au, 63 from UK</td>
<td></td>
<td>All</td>
<td>0.88 (0.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Au</td>
<td>0.91 (0.01)</td>
</tr>
<tr>
<td>Ko⁷ (2003)</td>
<td>USA</td>
<td>HALex</td>
<td>92</td>
<td>Measured acute&lt;1year,Short term (1-5 years) and longer term (&gt;5 years) following diagnosis</td>
<td></td>
<td>Acute</td>
<td>0.73 (0.29)</td>
</tr>
<tr>
<td>Killbridge⁸ (2001)</td>
<td>USA</td>
<td>Standard gamble</td>
<td>107</td>
<td>Patients with advanced melanoma receiving IFN</td>
<td></td>
<td>Disease free</td>
<td>0.96 (0.08)</td>
</tr>
<tr>
<td>Lear⁹ (2008)</td>
<td>Canada</td>
<td>Standard gamble</td>
<td>41</td>
<td>Patients with keratinocytic lesions undergoing various treatment modalities</td>
<td>0.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sebaratnam¹⁰  (2013)</td>
<td>Aus</td>
<td>Not provided</td>
<td></td>
<td>Patients undergoing treatment for BCC on head and neck. Value for recurrence of BCC</td>
<td>0.98</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Summary of published utility scores for excision of keratinocytic lesions**
<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Method</th>
<th>Description</th>
<th>Utility Range</th>
<th>SD</th>
<th>Mean Utility</th>
<th>Median Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shingler</td>
<td>UK</td>
<td>Time trade off</td>
<td>General public Scenarios rated using time trade off</td>
<td>0.67-0.94</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen</td>
<td>USA</td>
<td>Time trade off</td>
<td>Population patients 250 from 3 hospitals in US (n=182 for neoplasm and benign tumour)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lesion type</td>
<td>Number (% of total)</td>
<td>Mean utility</td>
<td>SD</td>
<td>Median utility</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Melanoma</td>
<td>2(1)</td>
<td>0.972</td>
<td>0.039</td>
<td>0.972</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neoplasm suspicious*</td>
<td>35(14)</td>
<td>0.971</td>
<td>0.047</td>
<td>0.996</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Benign tumour</td>
<td>17(7)</td>
<td>0.974</td>
<td>0.054</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NMSC</td>
<td>8(3)</td>
<td>0.976</td>
<td>0.052</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rule out BCC</td>
<td>8</td>
<td>0.974</td>
<td>0.040</td>
<td>0.997</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rule out kerat</td>
<td>10</td>
<td>0.979</td>
<td>0.036</td>
<td>0.997</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rule out Mel and DN</td>
<td>11</td>
<td>0.979</td>
<td>0.026</td>
<td>0.988</td>
</tr>
<tr>
<td>Littenberg</td>
<td>USA</td>
<td>Standard Gamble</td>
<td>74 patients (18 males, 56 females) who were attending a dermatology clinic who were</td>
<td>0.989</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naevus</td>
<td>6</td>
<td>0.975</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kerat</td>
<td>8</td>
<td>0.995</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>12</td>
<td>0.996</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Calculation of a utility score to use in Treeage for CE study

The summary table above show that health utility scores were lowest immediately after diagnosis/treatment and improve over time. The scores are also decrease with later stage of diagnosis although some anomalies are seen in Stage IV in some patient assessments. Because I am using a one year and then 2-5 year time period in the model, I propose to use the Tromme data and calculate a 12 month utility score using the initial utility for diagnosis and then add the surveillance utility score for the remaining months, then average out this value over 12 months to create a score that reflects diagnosis and treatment. The utility score for the subsequent period (2-5 years) will be based on the utility score for surveillance only and have no treatment component. For example, to calculate the 12 month utility score for the diagnosis of an insitu melanoma \( ((0.687*1)+(0.809*11))/12 = 0.799 \). I have not calculated a Stage IV score as no time period was provided. Any thoughts on valuing Stage IV?

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mean Utilities 1 year</th>
<th>Mean Utilities 2-5 year</th>
<th>95% CI for utilities by treatment and surveillance period</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 insitu</td>
<td>0.799</td>
<td>0.809</td>
<td>0.642-0.733 0.733-0.844</td>
</tr>
<tr>
<td>I</td>
<td>0.799</td>
<td>0.809</td>
<td>0.642-0.733 0.733-0.844</td>
</tr>
<tr>
<td>II</td>
<td>0.765</td>
<td>0.802</td>
<td>0.486-0.671 0.764-0.839</td>
</tr>
<tr>
<td>III</td>
<td>0.664</td>
<td>0.703</td>
<td>0.395-0.676 0.659-0.746</td>
</tr>
<tr>
<td>IV</td>
<td>0.583</td>
<td>0.583</td>
<td>0.524-0.642 0.708-0.833</td>
</tr>
</tbody>
</table>

**full health** = 1 as a score for normal health for one year. While some people may not be in full health, the score is based in relation to a melanoma diagnosis and treatment and we have assumed if utility scores for melanoma 0-1 then no melanoma =1
Appendix 9.5

Table 1. Clinics\(^1\) contacted for standard care billing practice when a patient books in for a skin check

\(^1\) Selection of clinics from Google after entering the words ‘skin cancer clinic’ and ‘GP super clinic’ and then random selection of practices from Sydney (City centre, North Sydney, Chatswood, Liverpool, Blacktown )and country areas Coffs Harbour, Broken Hill, Newcastle

<table>
<thead>
<tr>
<th>Clinic Type</th>
<th>Contact</th>
<th>First appointment</th>
<th>Subsequent appointment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin cancer Clinic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>City</td>
<td>9299 7777</td>
<td>54 or 36</td>
<td>23 or 36 or 53 or 54</td>
<td>First one is usually longer. Depends on time</td>
</tr>
<tr>
<td>Chatswood</td>
<td>9411 6199</td>
<td>23</td>
<td>23 or 36</td>
<td>Time related</td>
</tr>
<tr>
<td>North Sydney</td>
<td>9922 3844</td>
<td>23 or 53</td>
<td>23 or 53</td>
<td>Depends on the consultation time</td>
</tr>
<tr>
<td>Newcastle</td>
<td>4032 8700</td>
<td>36</td>
<td>23</td>
<td>Time based</td>
</tr>
<tr>
<td>Coffs Harbour</td>
<td>6651 9536</td>
<td>23 or 36</td>
<td>23 or 36 or 3</td>
<td>Depends on time occasionally use 44</td>
</tr>
<tr>
<td>Broken Hill</td>
<td>08 8088 7044</td>
<td>36</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Liverpool</td>
<td>9602 5785</td>
<td>104</td>
<td>105</td>
<td>Dr decides related to time</td>
</tr>
<tr>
<td><strong>GP super clinic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coffs Harbour</td>
<td>1300 364 375</td>
<td>36</td>
<td>36 or 23</td>
<td>Time based</td>
</tr>
<tr>
<td>Blacktown</td>
<td>8834 0222</td>
<td>36</td>
<td>36</td>
<td>Time based sometimes 23</td>
</tr>
<tr>
<td>Liverpool</td>
<td>9602 5785</td>
<td>36</td>
<td>23</td>
<td>Dr decides first could be 23 and subsequent may be 36</td>
</tr>
<tr>
<td>Sutherland</td>
<td>9542 6277</td>
<td>36</td>
<td>23 or 36</td>
<td>Dr decides could be 36 or 23, often other treatments</td>
</tr>
</tbody>
</table>

North Sydney, Chatswood, Liverpool, Blacktown )and country areas Coffs Harbour, Broken Hill, Newcastle

Table 2. MBS item numbers used by clinics. May be additional charge for patient

<table>
<thead>
<tr>
<th>MBS Item no.</th>
<th>Fee ($)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>16.95</td>
<td>Level A Professional attendance at consulting rooms</td>
</tr>
<tr>
<td>23</td>
<td>37.05</td>
<td>Level B Professional attendance by a GP, lasting less than 20 minutes</td>
</tr>
<tr>
<td>36</td>
<td>71.70</td>
<td>Level C Professional attendance by a GP, lasting at least 20 minutes</td>
</tr>
<tr>
<td>44</td>
<td>105.55</td>
<td>Level D Professional attendance by a GP, lasting at least 40 minutes</td>
</tr>
<tr>
<td>53</td>
<td>21.00</td>
<td>Standard consultation of more than 5 minutes duration but not more than 25 minutes duration</td>
</tr>
<tr>
<td>54</td>
<td>38.00</td>
<td>Long consultation between 25 minutes and 45 minutes</td>
</tr>
<tr>
<td>104</td>
<td>85.55</td>
<td>Initial attendance. Professional attendance at consulting rooms or hospital by a specialist in the practice of his or her specialty where the patient is referred to him or her</td>
</tr>
<tr>
<td>105</td>
<td>43.00</td>
<td>Subsequent attendance at consulting rooms or hospital by a specialist in the practice of his or her specialty</td>
</tr>
</tbody>
</table>

282