HEALTH TECHNOLOGY ASSESSMENT METHODS FOR EVALUATING MEDICAL TESTS: DEVELOPING A NOVEL APPLICATION OF THE LINKED EVIDENCE APPROACH

TRACY MERLIN

BA(Hons), MPH, AdvDip PM

School of Public Health

Faculty of Health Sciences

University of Adelaide

Submitted for the Degree of Doctor of Philosophy in Medicine

May 2015

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

BACKGROUND

The health consequences of medical testing are often not apparent or easily measured. To address this, the 'linked evidence approach' (LEA) was developed to estimate the clinical utility of a test so that policy makers can make informed public funding decisions. Australia has the largest international experience with the application of LEA.

RESEARCH AIM 1

The first aim of the presented research was to investigate the feasibility, utility and policy impact of LEA.

To enable the use of LEA in test evaluation there needed to be a more rigorous approach taken to determine the risk of bias in test accuracy studies. An existing evidence hierarchy recommended by the Australian Government for use in health technology assessment (HTA) was consequently revised between 2005 and 2009 to consider design-related biases in test accuracy studies. The hierarchy underwent a national public consultation and pilot process and became widely used.

A study was conducted to model the overall impact of LEA on health policy; data were extracted from HTA reports commissioned before-and-after the use of LEA was mandated by the Australian Government in 2005. Logistic regression analyses and regression diagnostics were performed to estimate model fit, model specification and to inform model selection. There was no discernible impact of LEA on the direction of public funding decisions (OR=1.36, 95%CI 0.62, 3.01) but the use of LEA *did* strongly predict that a medical test would *not* receive interim funding (X^2=12.63, df=1, p=0.0004). This suggests that the method enables greater certainty in decision-making.

RESEARCH AIM 2

The second aim was to develop guidance on how LEA should be *applied* during the evaluation of medical tests. A systematic literature review was performed on the methods used in HTAs evaluating medical tests so that a decision framework could be constructed to guide the application of LEA and to address potential methodological problems with the approach.

The framework systematises the application of LEA by categorising medical tests into three possible scenarios, namely optimisation, trade-off and disease-spectrum change. The evidence collation and linkage practices need to be tailored to each of these scenarios.

RESEARCH AIM 3

The final aim of the presented research was to adapt LEA to the evaluation of a drug and its companion diagnostic test ('personalised medicine').

An analysis of guidance documents and a review of case studies was undertaken to identify key information to guide decisions concerning the reimbursement of personalised medicines. An evaluation framework, incorporating LEA, was created to determine the safety, effectiveness and cost-effectiveness of personalised medicines. 79 evaluation items were proposed and examples provided to demonstrate the linkage of different types of evidence to reduce decision-maker uncertainty. The framework underwent a public consultation and pilot process.

The impact of the evaluation framework on public funding decisions was critically reviewed in the three years' after the framework was implemented nationally.

CONCLUSIONS

This thesis by publication resulted in three theoretical methods papers (published), one analytical paper (under review) and one published review paper (invited).

The methods developed for these publications were aimed at improving how medical tests are considered and valued by our health systems. LEA enables the clinical utility of medical tests to be estimated, leading to greater certainty for policy makers and reducing the need for 'interim' funding decisions. Methods for standardising the application of LEA have allowed consistent information to be provided to policy makers. The adaptation of LEA to the evaluation of personalised medicines has enabled previously siloed funding decisions on companion tests and therapeutics to be integrated.

The research outputs from this thesis have directly affected technology evaluation practice, with consequent impacts on health policy and test subsidy decisions.

DECLARATION

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

I acknowledge that the copyright of published works contained within this thesis (as listed on page xiii) resides with the copyright holder(s) of those works.

I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library catalogue, and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Signed: _____ *Dated:* _____

Tracy Merlin (Candidate)

ACKNOWLEDGEMENTS

Health technology assessment is a multi-disciplinary field characterised by collaboration and team work. As such, I would like to acknowledge each of the co-authors on my papers – this thesis would not be half as developed without having had the opportunity to discuss ideas and arguments with each of you; namely, Adele Weston, Rebecca Tooher, Claude Farah, Camille Schubert, Andrew Mitchell, Sam Lehman, Janet Hiller and Phil Ryan.

My sincere gratitude to those people in the Australian Government Department of Health who continually consider different and better ways to incorporate health technology assessment into policy. These public servants, and government advisory Committees of clinical experts and consumers, have a commitment to the public good that usually goes unrecognised but which has enormous health and economic implications for the Australian public at large.

My thanks to all of the wonderful people at Adelaide Health Technology Assessment (AHTA) for your understanding and support while I have been trying to get this PhD done – particular thanks go to Lashan Clifton, Skye Newton, Camille Schubert, Jacqueline Parsons and Shuhong Wang for holding the fort while I took study leave to 'write up'. Thank you also to Jackie Street and Taryn Bessen for digging me out of my AHTA hidey-hole every now and then.

To Dr Brian Stein who inadvertently set me on the path of evidence-based medicine and to A/Prof John Moss, who saw my potential as an academic, my sincere appreciation.

In 2007 I chose Prof Janet Hiller and Prof Phil Ryan as my supervisors because I respect them both immensely. The biggest motivation to complete the PhD was to not let them down. Thank you so much for your support and honesty.

Especial thanks to my very good friend, Nikki McCaffrey, for being there and sharing PhD horror stories, along with many other things; and to Greg, for always listening and showing me you care.

To mum, for instilling a love of books and learning; and to dad, for understanding what it means to strive.

Finally, and most importantly, this thesis is dedicated to the two young people who have lived through this PhD with me - **To my children, Caitlin and Alex**.

MANUSCRIPTS CONTRIBUTING TO THESIS

PUBLISHED

Merlin T, Weston A, Tooher R. Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Medical Research Methodology*, 2009, 9:34 doi:10.1186/1471-2288-9-34. Available at: http://www.biomedcentral.com/1471-2288/9/34

[Highly accessed designation by BMC Medical Research Methodology – 21,970 BioMed Central accesses; 103 citations in Google Scholar; 52 citations in ISI Web of Science (April 2015)].

Merlin T, Farah C, Schubert C, Mitchell A, Hiller JE, Ryan P. Assessing personalized medicines in Australia: A national framework for reviewing codependent technologies. *Medical Decision Making*, April 2013; 33(3):333-342.doi:10.1177/0272989X12452341. Available at: http://mdm.sagepub.com/content/33/3/333

[12 citations in Google Scholar; 6 citations in ISI Web of Science; 13 in Altmetric (measure of attention) which indicates the article is highly scored in this journal (ranked #22 of 369) and is in the top 25% of all articles measured by attention (April 2015)]

Merlin T, Lehman S, Ryan P, Hiller JE. The 'linked evidence approach' to assess medical tests: a critical analysis. *International Journal of Technology Assessment in Health Care*, July 2013; 29(3):343-350, doi: 10.1017/S0266462313000287. Available at:

http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=8955598

[4 citations in Google Scholar; 1 citation in ISI Web of Science (April 2015)]

Merlin T. The use of the 'linked evidence approach' to guide policy on the reimbursement of personalized medicines. *Personalized Medicine*, July 2014; 11(4): 435-448. Available at: http://www.futuremedicine.com/doi/abs/10.2217/pme.14.28

[Not yet cited]

UNDER REVIEW

Merlin T, Ryan P, Hiller JE. Impact of the 'linked evidence approach' method on policies to publicly fund diagnostic, staging and screening medical tests. *Medical Decision Making* [submitted May 2015].

CONFERENCE PRESENTATIONS ARISING FROM THESIS

INTERNATIONAL CONFERENCES

Methods

1. Merlin T, Mujoomdar M, Kisser A, Wurcel V. *Living in testing times: translating evidence on medical tests and companion diagnostics into reimbursement decisions.* Panel presentation. XII Annual Meeting HTAi 2015, Oslo, Norway, 15-17 June 2015.

2. Merlin T, Schubert C. *Evaluating medical tests for coverage decisions using the linked evidence approach.* Pre-conference full day workshop. XI Annual Meeting Health Technology Assessment international 2014, Washington DC, June 15 2014.

3. Merlin T, Farah C, Schubert C, Mitchell A, Hiller JE, Ryan P. *How to assess personalised medicines for reimbursement decisions? Developing a framework for Australia.* Oral presentation. IX Annual Meeting Health Technology Assessment international 2012, Bilbao, 25-27 June 2012.

4. Merlin T, Lehman S. *The benefits and flaws of the Linked Evidence Approach (LEA) to assess diagnostic and screening tests.* Poster presentation. VII Annual Meeting Health Technology Assessment international 2010, Dublin, 6-9 June 2010.

5. Merlin TL, Moss J, Hiller J. *Location, location, location – the impact of health care setting of technology use on both HTA results and funding policy.* Poster presentation. V Annual Meeting Health Technology Assessment international 2008, Montreal, 6-9 July, 2008.

6. Merlin T, Brooks A, Lord S, Hiller JE. *How to assess the effectiveness of a triage test in the context of direct versus linked evidence?* Poster presentation. 3rd Annual Health Technology Assessment international. July 3-5, 2006. Adelaide, South Australia.

7. Merlin T, Middleton P, Salisbury J, Weston A. *Ways to ensure evidence-based clinical practice guidelines are of high quality. Discussion workshop.* W52, p196. XIII Cochrane Colloquium, Melbourne, Australia. October 22-26, 2005.

8. Merlin T, Weston A, Tooher R (NHMRC "Levels" Working Party). *Re-assessing and revising "levels of evidence" in the critical appraisal process.* Oral presentation. O32, p.49. XIII Cochrane Colloquium, Melbourne, Australia. October 22-26, 2005.

9. Merlin T, Weston A, Tooher R. *Revising a national standard: redevelopment of the Australian NHMRC evidence hierarchy.* Italian Journal of Public Health (Supplement 1), Summer 2005, Year 3, 2(2): 156. [Oral presentation. Bringing HTA into practice. 2nd Annual Meeting, Rome. June 20-22, 2005]

Case studies

10. Vogan A, Schubert C, Parsons J, Morona J, Merlin T. *Assessing the cost-effectiveness of HBA1c testing in the diagnosis of type II diabetes and the impact of an imperfect diagnostic reference standard.* Poster presentation. Society for Medical Decision Making 36th Annual North American Meeting, Miami, Florida, 18-22 October 2014.
11. Vogan A, Schubert C, Parsons J, Morona J, Merlin T. *The impact of an imperfect diagnostic reference standard on the cost-effectiveness of HbA1c testing in the diagnosis of Type II diabetes.* Oral presentation. XI Annual Meeting HTAi 2014, Washington DC, 16-18 June 2014.
12. Kessels S, Schubert C, Newton S, Merlin T. *Assessment of catheter-free (wireless) ambulatory oesophageal PH monitoring for Gastro- Oesophageal Reflux Disease (GORD).* Poster presentation. XI Annual Meeting HTAi 2014, Washington DC, 16-18 June 2014.
13. Milverton J, Ellery B, Newton S, Kessels S, Merlin T. *CT colonography for those at high risk or symptomatic for colorectal cancer.* Poster presentation. XI Annual Meeting HTAi 2014, Washington DC, 16-18 June 2014.
14. Newton S, Wang S, Schubert C, Merlin T. *One small step for an individual, one giant leap for their family: considerations required for assessing the cost-effectiveness of genetic tests.* Oral presentation. X Annual Meeting HTAi 2013, Seoul, 17-19 June 2013.
15. Morona J, Newton S, Merlin T. *Genetic testing for VHL disease: limited benefit to the individual, but reduced surveillance for family members.* Poster presentation. X Annual Meeting HTAi 2013, Seoul, 17-19 June 2013.
16. Newton S, Fitzgerald P, Merlin T. *Mutation testing of the RET gene for MEN2.* Poster presentation. X Annual Meeting HTAi 2013, Seoul, 17-19 June 2013.
17. Buckley E, Merlin T, Mundy L, Hiller JE. *Molecular testing for myeloproliferative disease: The conundrum of an imperfect reference standard.* Poster presentation. VII

Annual Meeting Health Technology Assessment international 2010, Dublin, 6-9 June 2010.

18. Newton S, Street J, Merlin T, Hiller JE. *Is MRI effective for staging newly diagnosed rectal carcinoma? That depends on whether it changes management.* Oral presentation. VI Annual Meeting Health Technology Assessment international 2009, Singapore, 22-24 June, 2009.

19. Merlin TL, Newton S, Wang S, Hiller J. *Technology assessment in the context of workforce shortages and changing supply: digital mammography.* Oral presentation. V Annual Meeting Health Technology Assessment international 2008, Montreal, 6-9 July, 2008.

NATIONAL CONFERENCES

20. Merlin T. *Examining the challenges to health technology assessment from personalised medicine: the need for innovative approaches.* Australian Health Technology Assessment Conference, Sydney. November 26-27, 2012.

INVITED ADDRESSES ARISING FROM THESIS

INTERNATIONAL

1. Invited presentation. *Best practice in the evaluation of companion diagnostics (workshop)*. European Diagnostics Manufacturers Association. June 11, 2015, Brussels, Belgium.

NATIONAL

2. Training workshop. *Evaluating medical tests and co-dependent technologies for coverage decisions using the linked evidence approach*. Australian Government Department of Health. September 12, 2014, Canberra.
3. Invited Plenary Presentation. *Examining the challenges to health technology assessment from personalised medicine: the need for innovative approaches*. Australian Health Technology Assessment Conference, Sydney. November 26-27, 2012.
4. Training workshop. *Evaluating co-dependent technology submissions to inform PBAC decision-making*. Australian Government Department of Health and Ageing. October 26, 2012, Canberra.
5. Invited Panel Presentation. *Challenges for independent evaluation: MSAC assessments – past, present and future*. ARCS Scientific Congress, National Convention Centre, Canberra. August 2, 2011.
6. Invited Panel Presentation. *The FORM grading method: advantages and challenges*. National Health and Medical Research Council Guideline Development Symposium, Melbourne, June 29, 2011.
7. Invited Seminar Presentation. *Feasibility of the linked evidence approach when assessing diagnostic tests for public funding*. Screening and Test Evaluation Program (STEP) Seminar, University of Sydney, Sydney. March 16, 2011.
8. Invited Panel Presentation. *Rationale for proposed description of evidence needs*. ARCS Scientific Congress, National Convention Centre, Canberra. September 14, 2010.
9. Invited Plenary Presentation. *Developing a framework for co-dependent technologies for reimbursement.* Test Evaluation Symposium. NHMRC Clinical Trials Centre and

Screening and Test Evaluation Program (STEP), University of Sydney. Sydney. September 8, 2010.

10. Panel Discussion. *Better defining evidence requirements for medical tests.* Test Evaluation Symposium. NHMRC Clinical Trials Centre and Screening and Test Evaluation Program (STEP), University of Sydney. Sydney. September 8, 2010

11. Invited Plenary Presentation. *Personalised medicine initiatives*. Evidence-based Pathology Seminar. The Royal College of Pathologists of Australasia. Coogee Beach, Sydney. September 6, 2010.

LOCAL

12. PhD Progress Seminar. *Health technology assessment methods for determining the clinical effectiveness of diagnostic tests: an evaluation of the utility of the Linked Evidence Approach*. School of Population Health and Clinical Practice, University of Adelaide, May 16, 2012.

13. Invited Seminar. *Developing a national framework for evaluating personalised medicines*. Research Conversations, School of Population Health and Clinical Practice, University of Adelaide, November 24, 2011.

14. PhD Progress Seminar. *Feasibility of the Linked Evidence Approach (LEA) when assessing diagnostic tests for public funding*. School of Population Health and Clinical Practice, University of Adelaide, March 10, 2011.

15. Invited Seminar. *Investment and disinvestment in health technologies by policy-makers: An unusual case-study*. School of Population Health and Clinical Practice, University of Adelaide, February 6, 2009.

16. PhD Progress Seminar. *Methods for assessing diagnostic tests in a Health Technology Assessment (HTA) framework: Are they appropriate for triage tests II?* Discipline of Public Health, University of Adelaide, August 22, 2008.

17. PhD Progress Seminar. *Methods for assessing diagnostic tests in a Health Technology Assessment (HTA) framework: Are they appropriate for triage tests?* Discipline of Public Health, University of Adelaide, November 21, 2007.

ABBREVIATIONS

ACCE	Analytic validity, Clinical validity, Clinical utility, and Ethical, legal, social implications
AHRQ	Agency for Healthcare Research and Quality
AHTA	Adelaide Health Technology Assessment
AIC	Akaike information criterion
AUC	Area under the curve
CDC	Centers for Disease Control and Prevention
CEBM	Centre for Evidence Based Medicine
CE-mark	Conformité Européenne - mark
CED	Coverage with evidence development
CER	Comparative effectiveness research
CI	Confidence interval
CNV	Copy number variation
DMAC	Data Management and Analysis Centre
DNA	Deoxyribonucleic acid
EBM	Evidence-based medicine
EGAPP	Evaluation of Genomic Applications in Practice and Prevention
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin embedded
FISH	Fluorescent *in situ* hybridisation
FN	False negative
FP	False positive

G-I-N	Guidelines International Network
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBV DNA	Hepatitis B Virus Deoxyribonucleic acid
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Virus
HRM	High resolution melt method
HTA	Health Technology Assessment
HTAAP	Health Technology Assessment Access Point
HTAi	Health Technology Assessment international
ICER	Incremental Cost Effectiveness Ratio
IHC	Immunohistochemistry
INAHTA	International Network of Agencies for Health Technology Assessment
ITFOM	Information Technology Future Of Medicine
KIT D816V	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
K-RAS	Kirsten rat sarcoma viral oncogene homolog
LEA	Linked evidence approach
MBS	Medicare Benefits Schedule
MLPA	Multiplex ligation-dependent probe amplification
MSAC	Medical Services Advisory Committee
NATA	National Association of Testing Authorities
NHMRC	National Health and Medical Research Council
NHS CRD	National Health Service Centre for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence

NPV	Negative predictive value
NSCLC	Non-small cell lung cancer
OECD	Organisation for Economic Cooperation and Development
OR	Odds Ratio
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Schedule
PCR	Polymerase chain reaction
PCT	Pragmatic clinical trial
PDGFR rearrangements	Platelet-derived growth factor receptor
PhD	Doctor of Philosophy
PLAC	Prostheses List Advisory Committee
PPV	Positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	Randomised controlled trial
RNA	Ribonucleic acid
ROC	Receiver operating characteristic
RR	Relative Risk
SE	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
SNPs	Single nucleotide polymorphisms
SRDT	Systematic Reviews of Diagnostic Tests
SRE	Systematic review of evidence
SRT	Systematic review of trials
TGA	Therapeutic Goods Administration

TN	True negative
TP	True positive
UK	United Kingdom
USA	United States of America
USPSTF	United States Preventive Services Task Force