Psychosocial and clinical implications of genetic risk information about psychiatric disorders

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Psychosocial and clinical implications of genetic risk information about psychiatric disorders

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ABSTRACT

Despite international concern about unregulated genetic susceptibility testing, including genetic tests for risk of psychiatric disorders, there is surprisingly little data on the determinants of community interest in such testing, its psychosocial impacts and effect on health behaviour. This thesis is composed of a series of inter-related studies. Using major depressive disorder as an exmaple, the first study investigates public interest in genetic susceptibility testing for risk of, perception of potential for genetic discrimination, privacy issues, ethical implications and potential stigma resulting from genetic risk information about psychiatric disorders using qualitative and quantitative methodology (Studies 1A and 2A). This thesis then investigates how genetic risk information might be used in preventive health care using qualitative and quantitative methodology (Studies 1B and 2B). Finally, using mixed methods, this thesis investigates print media portrayal of psychiatric genetics to facilitate insights into how these issues are positioned on the public and political agenda (Study 3).

The findings demonstrated high community interest in genetic susceptibility testing for risk of major depressive disorder. Personal history of mental illness, self-estimation of being at higher than average risk for depression, belief that a genetic component would increase rather than decrease stigma and endorsement of perceived benefits of genetic testing positively and significantly predicted interest. The findings also showed that clinical services were the preferred mode of access for genetic susceptibility testing, with some interest in direct to consumer (DTC) genetic testing.

Despite finding attitudes that a genetic explanation for mental illness would increase rather than decrease stigma, there was strong community acceptance of depression risk genotyping. Healthy individuals were prepared to modify a genetic predisposition for major depressive disorder at a pre-symptomatic stage through preventive behaviours, although perceptions about whether environmental risk factors were modifiable varied. Target groups most likely to engage in such interventions were

those with a self-estimation of being at higher than average risk of major depressive disorder and those who endorsed the view that mental illness may develop from both genetic and modifiable environmental risk factors. The results suggest that genetic risk information has a potential value as an early intervention and preventive tool.

An over emphasis on optimism about perceived clinical benefits of genetic research in psychiatry and largely unfulfilled predictions about availability could encourage unrealistic expectations about future molecular-based treatment options.

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LIST OF ACRONYMS

5-HT	5-hydroxytryptamine receptor
5-HTTLPR	Serotonin-transporter-linked promoter region
ALDH2	Aldehyde dehydrogenase
ALRC	Australian Law Reform Commission
AHEC	Australian Health Ethics Committee
APOE	Apolipoprotein E
BRCA1	Breast cancer 1, early onset
CATI	Computer Assisted Telephone Interviewing
CNV	Copy number variants
DNA	Deoxyribonucleic acid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-IV
DTC	Direct-to-consumer
DZ	Dizygotic twins
FDA	Food and Drug Administration
FH	Familial hypercholesterolaemia
GxE	Gene by environment
GxG	Gene by gene
GAO	Government Accountability Office (USA)
GP	General practitioner (family physician)
GRIA3	Glutamate receptor 3
GRIK2	Glutamate receptor, ionotropic kainate 2
GRK3	G-protein receptor kinase 3
GST	Glutathione *S*-transferase
GWA	Genome-wide association
HNPCC	Hereditary non-polyposis colorectal cancer
ICD-10	International Statistical Classification of Diseases
IFSA	Investment and Financial Services Association
IVD	*in vitro* diagnostic (medical devices)
l/l	Long allele of the serotonin-transporter-linked promoter region
MTHFR	Methylenetetrahydrofolate reductase

MnSOD	Manganese superoxide dismutase
MZ	Monozygotic twins
NAT	*N*-acetyltransferase
NHMRC	National Health and Medical Research Council (Australia)
QSR N6	Qualitative Solutions and Research N6
REVEAL	Risk Evaluation and Education for Alzheimer (disease)
SCL6A4	Serotonin transporter gene
SNP	Single-nucleotide polymorphism
s/s	Short allele of the serotonin-transporter-linked promoter region
TGA	Therapeutic Goods Administration
WHO	World Health Organization

LIST OF PUBLICATIONS ARISING FROM THIS THESIS

STUDY 1A

Wilde A, Meiser B, Mitchell PB, Schofield PR. Public interest in predictive genetic testing, including direct-to-consumer testing, for susceptibility to major depressive disorder: preliminary findings. *Eur. J. Hum. Gen.* 2010; 18: 47–51

STUDY 1B

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STUDY 2A

Wilde A, Meiser B, Mitchell PB, Hadzi-Pavlovic D, Schofield PR. Community interest in predictive genetic testing for susceptibility to major depression in a large national sample. *Psychol. Med*. In press.

STUDY 2B

Wilde A, Meiser B, Mitchell PB, Schofield PR. Community attitudes to genetic susceptibility-based mental health interventions for healthy people in a large national sample. Australasian Society for Psychiatric Research annual conference handbook. 2009; p66. Submitted to *J Affect Disord.*

STUDY 3

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AWARDS

2008   The McConaghy Prize for Postgraduate Research for excellence in professional scientific communication.

LIST OF CONFERENCE PRESENTATIONS

International

2009   XVIIth World Congress on Psychiatric Genetics, San Diego, CA, USA. 4-8 November. Plenary symposium. 'Community interest in predictive genetic testing for susceptibility to major depression in a large national sample.' Funding: NHMRC Public Health Postgraduate Scholarship. Various grants via Philip Mitchell.

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2008   Centre of Society and Genomics Third International Workshop on Genetics, History and Public Understanding, held in conjunction with the 40th European Society for Human Genetics Annual Congress, Barcelona, Spain. 31 May-3 June. 'The impact of news coverage of the genetics of major depression, bipolar disorder and schizophrenia.' Funding: NHMRC Public Health Postgraduate Scholarship. Postgraduate Research Support Scheme, UNSW

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National

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INVITED PRESENTATIONS ARISING FROM THIS THESIS

National

2009   'Community interest in predictive genetic testing for susceptibility to major depression and impact on anticipated health behaviour'. 9 October. School of Psychiatry Academic Meeting, University of New South Wales, Sydney, Australia. Funding: NHMRC Public Health Postgraduate Scholarship.

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2008   'Psychiatric genetics in the Australian news media 1996-2006.' 18 April. Psychosocial Research Group, Prince of Wales Hospital, Sydney, Australia. Funding: NHMRC Public Health Postgraduate Scholarship.

2008   'The impact of news coverage of the genetics of major depression, bipolar disorder and schizophrenia.' 3 April. St George Hospital Academic Program, Sydney, Australia. Funding: NHMRC Public Health Postgraduate Scholarship.

2007   'Genetics in the news: media portrayals of the genetics of depression, bipolar disorder and schizophrenia.' 10 October. Faculty of Medicine, University of New South Wales, Sydney, Australia. Funding: NHMRC Public Health Postgraduate Scholarship.

LIST OF PUBLISHED ABSTRACTS

2009   **Wilde, A,** Meiser B, Mitchell PB, Hadzi-Pavlovic D, Schofield PR. Community interest in predictive genetic testing for susceptibility to major depression in a large national sample. *XVII World Congress of Psychiatric Genetics conference handbook* 2009. P2.4, p7.

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1 INTRODUCTION

Psychiatric disorders contribute half the leading causes of disability worldwide.[1] As a consequence of chronicity, psychiatric disorders are estimated to be the fourth most expensive disease group to national economies,[2] which is compounded by frequent co-morbidity with other diseases of global health significance. Major depressive disorder is the fourth leading cause of the global burden of disease and the leading cause of disability in adults aged 15 to 44 worldwide.[1, 3] The World Health Organization predicts major depressive disorder will contribute the second largest share of the global burden of disease by 2020, after ischaemic heart disease,[1] and become the leading cause of global disease burden by 2030.[3]

The WHO advises international governments to support mental health promotion by creating living conditions and environments that support mental health and allow people to adopt and maintain healthy lifestyles. It states that national mental health policies should not be solely concerned with mental health disorders, but also recognise and address the broader issues which promote mental health *per se*, such as preventive intervention.[4]

The United States National Institute of Mental Health, a component of the Department of Health and Human Services, plans to develop its research capacity towards risk prediction for mental disorders; develop interventions that pre-empt or interrupt the disease process; use knowledge about individual biological, environmental, and social factors for personalised interventions; and ensure that clinical research involves participation from the diversity of people and settings involved in health care.[5] As part of a strategic plan projected over the next five years, it aims to determine optimum timing for preventive interventions and develop new and better interventions that incorporate the diverse needs and circumstances of people with mental illnesses.

In the United Kingdom, mental illness accounts for more disability adjusted life years lost per annum than any other health condition.[6] The latest figures show that

20% of the total burden of disease was attributable to mental illness (including suicide), compared with 16.2% for cardiovascular diseases and 15.6% for cancer.[6] No other medical condition exceeds 10% of the total burden of disease. The UK Department of Health's recent mental health directive is to support the development of preventive interventions, facilitate early intervention, tackle stigma, enable personalised care and enhance innovation in mental health care.[6]

In Australia, one in five people have a lifetime risk of a mental illness.[7] The Commonwealth Department of Health and Ageing has identified a need for research evidence to identify potentially effective psychosocial interventions and prevention strategies; improve community mental health literacy; and encourage the media and primary care workers, particularly general practitioners (GPs), to play a major role in disseminating information with the goal of reducing barriers to seeking specialist care and reducing associated stigma.[8]

It is commonly accepted that psychiatric disorders result from the interaction of genetic susceptibility and environmental factors, such as chemical, infectious, physical, nutritional and behavioural factors.[9] With advances in genetic studies linking psychiatric markers to disease risk comes the potential to develop genetic tests for mental disorders, which usually begin in adolescence and early adult life.[10] Identification of genetically susceptible individuals at a pre-symptomatic stage offers an opportunity modify risk of mental illness among high risk groups through environment-specific preventive strategies. If such molecular-based preventive mental health interventions are to be successful, it is important that target risk groups understand the complexity of interactions between susceptibility genes of uncertain penetrance and environmental risk factors.

Interventions that rely on risk prediction have shown efficacy targeting youth at high risk of schizophrenia and other psychotic disorders, based on prodromal features of schizophrenia. Studies have shown that early pharmacotherapy and/or psychotherapy in these groups may delay or even prevent progression to a diagnosable psychotic disorder such as schizophrenia.[11] Genetic testing for

markers of mental illness has not been studied in prospective early intervention studies.

Family, twin, and adoption studies have demonstrated that major depressive disorder, bipolar disorder and schizophrenia are familial conditions. Evidence of a strong genetic component for psychiatric disorders comes from high heritability estimates for major depressive disorder (33%-48%),[12, 13] bipolar disorder (79%-83%),[14, 15] and schizophrenia (82%-85%).[16] Higher concordance rates in monozygotic (MZ) twins than dizygotic (DZ) twins in major depressive disorder (MZ 46%, DZ 20%),[12] bipolar disorder (MZ 43%, DZ 6%)[14] and schizophrenia (MZ 48%, DZ 4%)[16] confirms an important genetic component in the aetiology of these disorders, with part of the aetiology attributed to environmental factors.

Individuals with first-degree relatives with many of the mental illnesses are at increased risk for these disorders. Meta-analyses and reviews of family studies have shown a relative risk for major depressive disorder of 2.84 in first-degree relatives of affected probands with major depressive disorder compared to controls,[17] and a relative risk of 10.3 for bipolar disorder in first-degree relatives of probands with bipolar disorder compared to controls.[18, 19] Lifetime risk for major depressive disorder has been estimated at 5%–35% (females) and 5%–15% (males), which is increased to 10%–25% for probands with a first degree relative with this condition. Lifetime risk for probands with a first degree relative with schizophrenia has been estimated at 5%–16%.[20]

Recent evidence from genetic studies suggests allelic variation at common DNA polymorphisms accounts for variation in disease susceptibility.[21] Before genetic susceptibility testing (genetic tests that enable identification of individuals as being genetically susceptible to risk of future disease) for risk of psychiatric disorders can be implemented in clinical practice, it will be necessary to evaluate the analytic validity (capacity of the assay to reliably measure the genotype of interest reliably), clinical validity (the strength of the evidence for the link between genotype and disease) and clinical utility (the ability of the test to provide information that assists in the care of patients) of such tests.[22, 23]

Research into possibilities for molecular-based preventive interventions would further international and national goals and inform the design of communication and education strategies for the public, training materials for genetic and mental health clinicians, and the design and efficacy of early intervention and prevention programs, thus potentially contributing to reduction of the medical, social and financial burden associated with major depressive disorder, bipolar disorder and schizophrenia.

With an increasing focus on the genetic and biological basis for multifactorial disorders, there is an imperative to investigate the impact of genetic risk information on public understanding of psychiatric disorders and expectations of prospective uses of genetic information in psychiatry. Population research is necessary to evaluate psychosocial implications and attitudes towards genetic testing, to prevent its misuse and help realise its benefits.[24] However, genetic test results suggesting increased risk for a psychiatric disorder could increase stigma through negative social labelling. The question arises as to whether healthy asymptomatic people, particularly children and adolescents, should be tested.[25]

The availability of genetic susceptibility testing for multifactorial disorders is regarded as controversial because the predictive power of risk alleles is low and such tests are not currently linked to associated treatment.[26] Implications cited include a potential for a low-risk result to provide false reassurance, or a high-risk result to cause fatalistic thinking (beliefs that a disease will inevitably develop despite causality) based on a belief that a genetic component for a disorder makes the disorder less preventable.[27,28] Both circumstances could de-motivate an individual to engage in mental health interventions.[26]

Attitude studies show that genetic susceptibility testing for risk of a psychiatric disorder would be well received among members of families who have multiple relatives affected by bipolar disorder,[29-32] schizophrenia[33,34] or psychiatric disorders in general.[35] There is a deficit of research into the potential factors that would affect uptake of genetic susceptibility testing for psychiatric disorders and

willingness to engage in preventive health behaviours as a result of genetic status. There is also a lack of research into media portrayal of genetics and mental illness, and how well messages in the media match current scientific thinking. Given the highly influential nature of the media in shaping public attitudes,[36-40] media portrayal of the role of genetic risk information in managing psychiatric disorders is likely to influence community uptake of genetic susceptibility testing, health decisions and attitudes towards molecular-based preventive mental health interventions.

1.1   Aims of the thesis

This thesis aims firstly to improve understanding of community acceptability of genetic susceptibility testing for psychiatric disorders and preferences for how such testing should be accessed. Using depression risk genotyping as an example, the thesis aims to examine these issues by evaluating perceived benefits and limitations of genetic susceptibility testing for risk of depression and assessing the impact of genetic risk information about mental illness on beliefs about stigma associated with these disorders. Secondly, it aims to determine whether healthy individuals with a genetic predisposition for major depressive disorder are prepared to modify their risk at a pre-symptomatic stage through preventive behaviours, although perceived modifiability of environmental risk factors is variable. Finally, to gauge public thinking on these issues, this thesis aims to identify how the media has portrayed a genetic basis for mental illness in print articles published between 1996 and 2009. Hereby, it is intended that the findings from this thesis will provide insight into anticipated public response to genetic susceptibility testing in psychiatry, if it becomes available, and to inform the design of molecular-based preventive mental health interventions for healthy people with a genetic susceptibility.

1.2 Overview of the thesis

1.2.1 Chapter 2

Chapter 2 is a literature review of genetic studies; genetic susceptibility testing; its hypothetical impact on the public; impact of genetic risk information on individuals and families with psychiatric disorders and impact of disclosure of genotype. It also critically reviews the current situation regarding DTC genetic susceptibility testing marketed by international commercial biotechnology companies. It reviews the literature about preventive interventions based on genetic risk information for multifactorial disorders; describes impact of genetic risk information on discrimination, privacy and stigma; and examines the ethical issues surrounding use of genetic information. This chapter also reviews media analyses about the portrayal of psychiatric genetics and genetic testing in the Australian print news media. Finally, this chapter reviews literature concerning public health implications of genetic susceptibility testing and provides an overview of current legislative and regulation issues regarding genetic susceptibility testing, including tests marketed directly to the consumer.

Chapters 3-7 provide a series of three inter-related studies.

1.2.2 Chapter 3

Rapid advances in genetic studies and identification of 'risk' polymorphisms for psychiatric disorders have produced an imperative to evaluate public attitudes towards the complexity of genetic risk prediction in psychiatry involving susceptibility genes, uncertain penetrance and gene-environment interactions on which successful molecular-based preventive mental health interventions will depend. Chapters 3 and 4 describe a qualitative study using focus group methodology which explored the views of members of the community unselected for depression risk. Chapter 3 describes the study's findings on attitudes towards genetic susceptibility testing, including views about DTC genetic testing available

from commercial biotechnology companies, using depression risk genotyping as an example. It also analyses views on stigma, discrimination and DNA privacy related to genetic risk information about psychiatric disorders.

1.2.3   Chapter 4

The rapid expansion of commercial genetic susceptibility tests for multifactorial diseases marketed DTC, including tests involving psychiatric disorders, has raised urgent questions regarding how the public might use genetic risk information to change health behaviour. Chapter 4 describes the findings from the focus group study on public understanding of the aetiology of mental illness and preparedness of participants to engage in preventive mental health interventions based on a hypothetical risk for major depressive disorder.

1.2.4   Chapter 5

Despite current international concern about unregulated genetic susceptibility testing, few studies have evaluated both the determinants of community interest in such testing and its psychosocial impacts in large national samples. Chapters 5 and 6 describe a quantitative study that provides data from a large cross-sectional survey of a randomly selected national population sample unselected for depression risk. Chapter 5 reports the findings on public attitudes towards genetic testing for depression risk, if they were available. Preference for access to such tests via a clinician or DTC is reported. The findings from the qualitative study 1A reported in Chapter 3 were used to inform the hypotheses that were tested in this study.

1.2.5   Chapter 6

No large population studies have examined how genetic risk information involving psychiatric disorders might be interpreted and used by consumers. Chapter 6 describes the findings of a quantitative on preparedness of participants to engage in preventive mental health interventions based on a hypothetical genetic risk for major depressive disorder. The quantitative analysis of the findings is guided by

the theoretical framework of Leventhal's Common Sense Model of Self-Regulation.[41] The findings from the qualitative study 1B reported in Chapter 4 were used to inform the hypotheses that were tested in this study.

1.2.6 Chapter 7

Since the media influences public understanding, health decisions and uptake of genetic technology and is influential in the development of policy,[42, 43] analysing the media portrayal of psychiatric genetics provides an indication of the importance of the topic on the public and political agenda. Chapter 7 describes a study that qualitatively analysed media content and framing of psychiatric genetics and genetic testing. This study includes a broad sample of Australian print media across a 14 year period.

1.2.7 Chapter 8

Chapter 8 provides an overview of the empirical studies undertaken as part of this thesis, a summary of the major findings and a discussion of the implications of the findings for the future of genetic susceptibility testing in psychiatry. It includes a research agenda that aims to provide possible suggestions from research that may inform future genetic testing services. Limitations of the current thesis are discussed. and suggestions for improving validity of the data conclude the chapter.

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2   REVIEW OF THE LITERATURE

2.1   Literature search strategy

The body of literature reviewed in this thesis was identified by searching the following databases: Medline via Ovid, PsycINFO, Psychiatry Online, Expanded Academic Index, APAIS health, Proquest, JSTOR and library catalogues using the following search terms: genet*, gene, genes, DTC, "direct to consumer", "mental illness", psychiatr*, depression, "major depressive disorder", "manic depression", "bipolar disorder", schizophrenia, "genetic counselling" and psychiatr*. Hand searching of reference lists of relevant publications retrieved additional literature for references, and searches of authors with a track record in this field were also conducted. These searches identified a body of research on the genetics of the three target psychiatric disorders, including their psychosocial and public health implications. For the literature review of the media analyses, further literature searches using the terms media, analysis, media discourse, content analysis and framing analysis in conjunction with the above terms produced literature examining media coverage of medical genetics including the few analyses of psychiatric genetics available in the media.

2.2   Genetic studies

Current scientific thinking proposes that the aetiology of most psychiatric disorders involves a combination of multiple genes and environmental factors.[1] Unlike Mendelian single gene disorders with dominant or recessive modes of inheritance, psychiatric disorders are genetically complex, involving risk alleles of small effect size.[2] Although an individual with a high-risk allele may only have a slightly increased chance of developing the disorder, alleles involved in psychiatric

disorders are considered to be of public health significance, because high allele frequencies in the population means a large proportion of people may be affected.[2]

Few studies have systematically investigated the role of epigenetic factors in psychiatric disorders. Epigenesis is not clearly defined but is thought to occur due to dna methylation during key developmental periods such as embryogenesis which may determine the long-term function and expression of genes.[3] It is hypothesised that if dna methylation occurs *in utero,* gene expression may be altered not only in the developing fetus but may be inherited by the fetus's future offspring even though the genetic sequence itself is not changed. Epigenetic factors could in part explain why mental illness appears to aggregate in families where no single causative gene has been found. Further, epigenetic variation may explain discordance for mental disorders in monozygotic twins raised in the same environment. Currently, there is little conclusive genetic evidence for epigenesis in the development of mental illnesses[4]

The aim of this section is not to discuss in detail the status of current genetic findings in psychiatry, but rather to provide a background within which the potential development of genetic susceptibility tests for psychiatric disorders has arisen. Prior to commencement of this thesis, genetic research in psychiatry focused on associations between single-nucleotide polymorphisms (SNPs) in specific genes and mental illness. Numerous genetic studies reported SNPs associated with major depressive disorder, (e.g.[5, 6]) bipolar disorder (e.g.[7-9]) and schizophrenia (e.g.[10]).

In 2003, Caspi et al.[5] reported an interaction between a functional polymorphism in the promoter region (*5-HTTLPR*) of the serotonin transporter gene (*SCL6A4*) and experience of stressful life events in increasing the likelihood of a major depressive disorder in non-clinical populations. The study found evidence that homozygosity for the short allele (*s/s*) of the serotonin transporter gene-linked polymorphic region conferred highest risk for depression on exposure to multiple stressful life events, with the lowest risk seen among individuals homozygous for the long allele (l/l). A large number of studies replicated the association in adults,

(e.g.[6, 11-13]) adolescents[14] and children,[15,16] with some failures to replicate (e.g.[17-19]) and some studies finding a reverse association,[20, 21] in that susceptibility was related to the *l* rather than *s* allele. Several of these studies suggested that the *s/s* variant may play a role in mediating response to stress, with *s/s* individuals demonstrating hyper-reactivity to stressors and/or deficient problem-solving coping, which may convey increased risk to future major depressive disorder[5, 6, 11, 12, 14, 15] but is not a risk factor by itself .[22]

The predictive value of the *5-HTTLPR* polymorphism remains unclear since unknown gene-gene interactions may contribute to effect and the environmental contribution has not been quantified. However, the apparent reproducibility of the *5-HTTLPR* polymorphism, at the time of commencing this thesis in 2006, presented a good example upon which to gauge public attitudes towards genetic susceptibility testing and preventive interventions based on individual risk.

The publication of two meta-analyses[23, 24] in 2009, subsequent to the completion of data collection for this thesis, fuelled debate in the psychiatric research community about the robustness of the association between the *5-HTTLPR* polymorphism, stressful life events and depression. Neither meta-analysis confirmed evidence from individual studies that the serotonin transporter genotype increased risk for depression. Risch and colleagues[23] combined data from 14 prior studies resulting in a sample of 14, 250 participants. Its strengths were the very large combined sample, rigorous methodology and remodelling the included studies to fit Caspi's original genetic model. Despite requiring strict inclusion criteria (e.g. depression measures using Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) or International Statistical Classification of Diseases, (ICD-10) and stressful life event measures using Brugha List of Threatening Experiences), there were inconsistencies in applying these criteria.[25, 26] Depression scales and stressful life event measures varied greatly between the included studies including variation in self reporting and objective measurement.

Caspi et al[26] point out that most non-replications included in the meta-analyses[23,24] used brief self-report measures of stress, whereas replicated studies used face-to-

face interviews to assess stress exposure, which presented opportunity to objectively measure a reported stressful event. Rutter and colleagues[25] highlighted other inconsistencies in the meta-analyses[23, 24] such as lack of agreement about which genetic model the studies used, and discrepancies in determining which stressful life events to focus upon. Studies included in the meta-analysis[23] that focused on two specific stressors that are established causes of depression, childhood maltreatment and medical illness, consistently generated replications, while studies that relied on non specific adverse life events produced mixed results.[26] They also argued that the statistical focus of the meta-analysis was not adequate to elucidate biological processes involved in GxE interactions such as the synergistic and cumulative effect of stressful life events in shaping depressive phenotype, and the limitations of a meta-analysis in testing for a possible gene x gene (GxG) interaction to account for the observed GxE effect.

Furthermore, one meta-analysis[23] excluded at least 10 studies that had replicated the association, some of which fitted the inclusion criteria on the basis of the categorical measures of depression and stressful life events stated. Munafò and colleagues[24] included 33 studies in their meta-analysis, of which the authors[26] claim only a minority reported a replication that was comparable to that in the original report by Caspi et al.[5]

These limitations could account for why many genetic studies alone have shown a clear positive association between the *5-HTTLPR* polymorphism, stressful life events and depression, while combined data has shown no association. Contradictions between the results of genetic studies could be in part explained by small sample size of studies attempting replication, which may overestimate the true effect of the allele.[27] Rutter and colleagues concluded that further research is needed to allow understanding of how *5-HTT* allelic variations affect response to stressors.[25]

Limitations associated with small sample sizes and small SNP effect sizes may be overcome by current genome-wide association (GWA) studies, which have the capacity to analyse 500,000 to 1,000,000 SNPs, thereby generating large datasets

that facilitate the potential to identify novel causative SNPs anywhere in the genome. Recent evidence from GWA studies suggests that the major contribution to the heritability of risk for psychiatric disorders comes from the combined effect of a number of common SNPs, each of which alone contributes only a small effect.[61-63] For example, for bipolar disorder, GWA studies have found a small number of genes associated with bipolar disorder that only account for 1% of the genetic variance,[28] but research continues to identify new molecular pathways that reveal small effects in multiple genes, which when combined, may offer greater predictive value.[29] Recently, GWA studies have detected associations between common SNPs and rare copy number variants (CNV) and psychiatric disorders.[30, 31] CNVs, segments of DNA in which copy number differences have been found by comparison of two or more genomes, are believed to increase risk to a particular disorder.[30, 31] It is anticipated that the results of current meta-analyses of GWA studies involving major depressive disorder, bipolar disorder and schizophrenia will provide more robust evidence for genetic pathways involved in psychiatric disorders than previously available.[32]

2.2.1 Conclusions

Genetic susceptibility testing for risk of psychiatric disorders is currently premature since polymorphism-disorder associations thus far have uncertain clinical validity and predictive power. Evidence from GWA studies suggests genetic susceptibility testing in psychiatry will be a possibility in the future by combining the predictive power of multiple genome-wide markers to determine definitive genetic risk algorithms for psychiatric disorders.

2.3 Genetic susceptibility testing

More than 1600 genetic tests were available to patients and the public in 2010 (www.nih.gov). In addition to predictive (pre-symptomatic) testing, these genetic tests included newborn screening, diagnostic testing, carrier testing, prenatal and

pre-implantation testing. Genetic susceptibility testing may enable high risk individuals to make informed reproductive and/or health care decisions. Predictive genetic tests for single-gene disorders with fully penetrant alleles (e.g. Huntington disease) or multifactorial disorders with highly penetrant alleles (e.g. inherited breast cancer) are well established in clinical settings. Confusion about the meaning of the result of a predictive genetic test can occur even where risk probabilities are well defined. For example, discrepancies have been reported between patients' and health professionals' perceptions of risk for Huntington disorder,[33] possibly due to complexities of understanding the meaning of variation in the number of triplet repeats. For familial cancers, with high risk probabilities of 55%-85%,[34] which should enable test recipients to make informed decisions about regular screening and surgical preventive interventions, difficulties have been reported among test recipients in understanding the meaning of such numerical risk probabilities.[33]

Interpretation of the results of genetic susceptibility tests for multifactorial disorders involving multiple alleles each with small effect and uncertain penetrance (e.g. heart disease, diabetes and mental illness) present special difficulties in risk interpretation and communication. Before genetic susceptibility tests for multifactorial disorders with genetic and environmental aetiology, including psychiatric disorders, become widely available, it is imperative that the scientific evidence for genetic markers is robust and that patients and the public understand that such genetic tests do not provide absolute information about risk.

2.3.1   Direct-to-consumer (DTC) genetic susceptibility testing

DTC genetic tests are considered to be genetic tests that are used in the home or a similar environment and are not carried out under the supervision of a health care provider.[35] Advances in genetic studies proclaiming genetic associations with an increasing number of disease polymorphisms has led to commercialisation of genetic tests. The development of high throughput technology means laboratories can rapidly sequence hundreds of thousands of SNPs. By 2008, there were estimated to be about 1400 DTC predictive genetic tests and genetic susceptibility

tests on the market,[36] some of which are detailed by Melzer et al.[37] DTC tests for multifactorial disorders with small effect alleles presents issues regarding communicating risk to the test recipient and interpretation of the test result.[38] Some genetic susceptibility tests are already being developed in commercial settings for multifactorial disorders with insufficient evidence for their clinical validity and clinical utility (see Chapter 2.3.1).

One of the earliest DTC genetic testing ventures arose in March 2002 in the UK, when Sciona Laboratories marketed nutrigenomic genetic tests via prominent retail chain stores (e.g. The Body Shop). Sciona offered personalised dietary information based on variants of methylenetetrahydrofolate reductase (*MTHFR*), manganese superoxide dismutase (*MnSOD*), cytochrome P450, *N*-acetyltransferase (*NAT*), glutathione *S*-transferase (*GST*) and aldehyde dehydrogenase (*ALDH2*) genes purported to be linked to nutritional deficiencies. The scientific evidence for these claims was at the time inconclusive. For £120 per genetic test, customers received dietary recommendations based on their genotype. However, recommendations provided were already part of national nutritional guidelines. Like many DTC vendors of genetic susceptibility tests, the company disproportionately emphasised the importance of genes in determining health,[39] while minimising environmental and social determinants of health. Many start-up DTC genetic testing companies were accepting orders that bypassed consumers' own doctors, leaving consumers at risk of selecting inappropriate tests, misinterpreting results and making inappropriate health and lifestyle decisions. During the same year, the UK Human Genetics Commission commenced investigations into DTC genetic testing in the UK, and by 2003, Sciona relocated to Boulder in Colorado, USA. Sciona was one of the companies criticised in an investigation of genetic tests by the US Government Accountability Office (GAO) in 2008, as described in Chapter 2.10.[40] The company ceased trading in May 2009.

In 2006, at the time of conception of this thesis, there was an upsurge of start-up biotechnology companies offering DTC genetic tests, particularly in the US and Europe, including tests for risk of major depressive disorder, bipolar disorder and schizophrenia. Some genetic tests marketed DTC were already available in clinical

practice, for example, predictive genetic tests to identify mutations of single gene disorders such as Tay Sachs disease. However, many tests offered DTC for multifactorial disorders lacked published data to support clinical validity. One of these was a "depression risk genetic test" marketed online by NeuroMark Genomics (www.neuromark.com) of Boulder in Colorado. The product was marketed after several genetic studies had replicated Caspi's[5] 2003 landmark study involving an interaction between *5-HTTLPR,* exposure to stressful life events and major depressive disorder, as discussed in Chapter 2.2. The commercial availability of such a test raised concerns among the psychiatric research community since the predictive power of the test and the interpretation of results were not established, nor was there a clear indication of its clinical utility.[41] Marketing claims included reassurance to those receiving 'low risk' genotype result, which could generate complacency about risk, and failure to acknowledge the role of non-genetic factors in the aetiology of multifactorial disorders. Although NeuroMark required a referral for the test from a doctor, the company provided their own staff psychiatrist for this purpose. A disclaimer by the company's chief executive officer, Kim Bechthold, stated that the purpose of the test was "educational," and that it was not intended as a tool to assist in the diagnosis of depression. By December 2006, the company had withdrawn the genetic test, claiming contrarily that this was due to "enormous demand" and noted plans to reintroduce the test in mid-2007. At the time of writing, in 2010, the test had not been relaunched.

Another development in commercial DTC genetic testing was in pharmacogenomics, the clinical testing of genetic variation that gives rise to differing response to medications. In 2006, a US company, Prediction Sciences (www.predict.net/Prediction_Sciences/Home.html), based in La Jolla, California, was granted $482,000 from the National Institute of Mental Health to support the development of a diagnostic genetic test to predict patient response to the mood stabiliser lithium and the antipsychotic medications, olanzapine and aripiprazole,[42] to help tailor the treatment of bipolar disorder. At the time of writing this thesis, Prediction Sciences had not yet launched the test to the consumer. NeuroMark was developing similar services designed to predict suicidal ideation in response to the

anti-depressant medication citalopram. At this time, one study had found markers within the genes *GRIK2* (glutamate receptor, ionotropic kainate 2) and *GRIA3* (glutamate receptor 3) were significantly associated with treatment-emergent suicidal ideation during citalopram therapy.[43] However these findings have not been replicated.

With the development of genome-wide DNA analysis by 2007, several new companies launched DTC whole-genome testing, including the high profile companies 23andMe (www.23andme.com) in Mountain View, California, USA; deCODE Genetics (www.decode.com) of Reykjavik, Iceland; and Navigenics (www.navigenics.com), based in Foster City, California. Using the same SNP chips that were being used in GWA studies, biotechnology companies could now readily scan a million SNPs across the whole genome.[30] This advance did not offer any greater power in the prediction of future disease, as SNP-based whole-genome information was still only linked to small increases in the risk of major diseases in the range of only 5-30%.[44]

Few scientific studies at that time had critically evaluated the scientific evidence underlying gene-disease associations that were being offered as 'predictive' genetic tests to the public. The first study[45] to rigorously review the evidence from association studies and meta-analyses underpinning several polymorphism-disease associations, including depression and schizophrenia, examined 69 polymorphisms of 56 different genes tested commercially by seven biotechnology companies. The authors found that less than half of the 56 genes had significant associations with disease risk, and many of these (24) had not been subject to meta-analysis. Of the 160 polymorphism-disease associations that were reviewed in meta-analyses, only 60 were found to be statistically significant. Of the associations that were statistically significant, the odds ratios were modest, ranging from 1.0 to 3.2 (CI 95%) for risk variants. This study highlighted major concerns that most health advice offered by DTC biotechnology companies appeared to be based on the purported risk status of single rather than multiple genetic markers, which most studies have shown to have a small effect by themselves. They also found that some polymorphisms increased the risk for some diseases and decreased the risk

for others, which could contradict the appropriateness of health interventions. This study adds support to concerns about the clinical validity of genetic services currently offered DTC and the potentially adverse impact on consumer health decisions.

During the empirical phase of this thesis, several start-up companies began developing or marketing DTC genetic tests for the risk of psychiatric disorders and the risk of suicidal ideation in response to medication. Psynomics based in San Diego, California (psynomics.com/index.php), began marketing two DTC 'bipolar tests,' one of which purported to identify increased risk for bipolar disorder, the other to assess patient response to psychotropic medication for bipolar disorder. These tests were based on several studies of SNPs in the *GRK3* (G-protein receptor kinase 3) gene on chromosome 22.[9, 10, 46] The studies reported that the SNPs were associated with a doubling or tripling of risk for bipolar disorder, although this finding has not been replicated by other studies. A major GWA study found no evidence of a GRK3-bipolar disorder association.[47]

In a report published in *Science* in 2008,[48] the chief executive officer of Psynomics, John Kelsoe, admitted that evidence for a *GRK3*–bipolar disorder association was flimsy but explained that Psynomics was a business model that is market-driven, expecting to sell 1800 tests in 2008 and 30,000 by 2013. The report also named two other biotechnology companies that planned to market psychiatric genetic tests by 2009. One of these was SureGene based in Louisville, Kentucky, USA (www.suregene.net/home.aspx), which planned to launch a genetic test for the risk of psychosis and another to predict response to antipsychotics. The other was NeuroMark, which appeared to have abandoned the *5-HTTLPR* test, and now planned to market a pharmacogenomic test for the risk of suicidality in response to the anti-depressant citalopram. By 2010, none of these biotechnology companies were accepting orders.

Commentators have questioned the scientific accuracy of DTC genetic susceptibility tests since several individuals reported receiving different predictions from different DTC companies for the same disease.[49] To test this, a

team from the J. Craig Venter Institute compared results from 23andMe and Navigenics for 13 diseases for five individuals.[49] After removing the variable for average population risk, they found for seven diseases, only 50% or less of the predictions agreed between the two companies across the five individuals. The findings suggest that DTC genetic tests should be used with caution. The authors report discrepancies may also include differences in risk reporting between companies, such as absolute risk versus relative risk; differences in the criteria used for accepting a marker reported in genome-wide association results into relative risk calculations; the use of different markers for each disease in risk calculations; and variations in average population risk calculations.[49] Both Navigenics and 23andMe received California Department of Public Health cease-and-desist letters (see Chapter 2.10). Since they have both been granted licences after complying with protocol and continue to operate their DTC genetic testing services,[50] discrepancies in scientific validity of genetic test results from such DTC companies are a major cause for concern.

Such concerns stimulated a flurry of subjective commentaries the *Lancet, New England Journal of Medicine, Nature* and other journals.[51-54] Commentators universally agreed that marketing of such genetic tests was premature and argued that too little was known about the genetic risks for complex diseases to offer meaningful information about health risk or how such information could be used to reduce risk for disease and promote preventive health behaviours.

Nevertheless, Navigenics has expanded its interests and launched two large scale initiatives to examine the impact of genetic test results on behaviour and scope for health interventions. One of these is a 20-year longitudinal study, launched in December 2008 in collaboration with Scripps Translational Science Institute, Affymetrix Inc and Microsoft. The Scripps Genomic Health Initiative (www.navigenics.com/partners/scripps) recruited 10,000 Scripps employees, their families and friends who paid US$300 (full price US$2,500) for a "whole genome" scan to determine risk for 23 health conditions including type 2 diabetes, Alzheimer disease, heart attack, obesity, rheumatoid arthritis, multiple sclerosis and some cancers. The initiative proved so popular that since filling the study

recruitment quota, Navigenics now offers discount "genome scans" to Scripps employees (www.navigenics.com/scripps).

In 2010, Navigenics launched a further genome scanning initiative by teaming with Australian health insurance company NIB (www.NIB.com.au) to provide a limited offer of "heavily discounted" "whole genome" testing for 5,000 of NIB's customers at US$499 (AUD$550), (full price US$999). Genetic tests included risk for Alzheimer disease, heart disease, colon, lung, prostate and breast cancer (although not BRCA1 or 2), and type 2 diabetes, as well as individual response to certain medications (www.nib.com.au/home/newtonib/whynib/Pages/Genetic_Testing_and_your_healthcare.aspx)

Both initiatives have raised serious ethical concerns about the responsible use of genetic information. Marketing claims by Navigenics and other DTC genetic testing companies do not match current scientific evidence about the predictive power of the majority of the tests offered.[45] Navigenics claims genome testing will have no impact on NIB customers' health insurance, but fails to mention the potential risk of discrimination for life insurance (which NIB also sells), income protection insurance and in employment. Thus far, there is no legislation in Australia to protect NIB customers or other individuals purchasing genetic susceptibility tests from genetic discrimination (see Chapter 2.10). It is unknown how individuals will use genetic information obtained from DTC genetic companies about predisposition to disorders with uncertain penetrance. Typical marketing literature includes one or two isolated case studies in which individuals claim they benefited from genome testing by discovering a predisposition to, for example, celiac disease, and subsequently increased disease monitoring, for example, by having an endoscopy, and on finding pathology, obtained early treatment. The company does not offer any data showing neutral or negative health behavioural outcomes. The results of the 10,000 person study of genotyping and health behaviour funded by Navigenics and its business partners with vested financial interests in promoting DTC genetic testing services will likely be limited by conflicts of interest. Large independent studies are urgently required to inform recommendations for the use of DTC genetic tests in preventive medicine.

2.3.2 Conclusions

Lack of regulation of the DTC genetic testing industry enables private companies to exploit genetic testing services at the risk of causing serious harm to the health of the consumer. The potential danger of marketing health recommendations to people with 'high risk' profiles is that those with 'low risk' profiles could mistakenly believe that they have little need to make healthy lifestyle changes. Furthermore, the gap between 'high risk' and 'low risk' status is potentially narrow, given the low predictive power of SNPs alone, rendering 'high risk' status not particularly meaningful in terms of health interventions.

Rapid progress is being made in molecular genetics research, which makes it likely that many more common variants conferring a risk of disease will be identified in the coming years. While this could lead to increasing stability of individual risk estimates, DTC genetic testing services offered by biotechnology companies could undermine such advances if discrepancies in clinical validity of their tests continue. Premature unregulated DTC availability of genetic susceptibility testing for risk of psychiatric disorders could undermine public confidence in future evidence-based clinical psychiatric genetic services.

2.4 Psychosocial impact of genetic risk information about multifactorial disorders

Since genetic tests are not currently available for multifactorial disorders involving genes of uncertain penetrance, little is known about potential psychosocial impact of such tests. Studies have examined public attitudes towards genetic risk information about various disorders using hypothetical scenarios of genetic testing and impact of perceived genetic risk among families affected by psychiatric disorders. Studies assessing the impact of genetic test results have thus far predominantly focused on Huntington disease[55] and familial cancers.[33, 56]

It has been hypothesised that disclosure of genetic status for risk of a complex multifactorial disorder has a lower impact among individuals with a family history of that disorder than among those without.[57] The rationale is that when people with a family history undergo genotyping there is some degree of expectation of having the higher-risk allele, thus reducing the impact of an unfavourable result. with the Little direct empirical evidence is available that has examined this hypothesis. Among women with newly diagnosed with breast cancer without a family history of hereditary breast cancer, genetic testing was found to predict long-term distress.[58, 59]

2.4.1   Impact of hypothesised genetic risk on public attitudes and perceptions

A sizeable body of literature is available on attitudes to genetic testing for adult-onset disorders; many of these studies presented participants with the scenario of a hypothetical genetic test indicating one's own increased risk for a disorder, using heart disease,[60,61, 62] arthritis,[60] diabetes,[62] lung cancer,[62] colon cancer[62] and nicotine dependence,[63] as examples.

When the authors presented the statement "a gene for heart disease" to members of focus groups, participants perceived heart disease as having both genetic and environmental causal attributions. The statement triggered endorsement of the concept of genetic fatalism less frequently than the authors expected.[61] This study also identified perceptions that genetic testing would facilitate opportunities for intervention and patient education to optimise modifiable behavioural and environmental risk factors.[61] In contrast, another study found that framing risk for heart disease or arthritis as 'genetic' compared to 'unspecified' risk resulted in greater endorsement of genetic rather than environmental causal attributions.[60] Genetic risk information also prompted fatalistic beliefs that the disorder was less preventable compared to when the source of the risk was unspecified. The latter findings suggest that opportunities to encourage individuals to modify their environmental and behavioural risk factors could be compromised if the provision of genetic risk information induces fatalistic beliefs.

Both studies were limited by the small group setting and the hypothetical nature of the investigation, which prevents extrapolation of the findings to the clinical setting. Patient responses may differ from these findings when faced with an actual genetic test result. Interpersonal interaction with a genetic counsellor and a genetic test result that could have a real impact on one's life is likely to affect response to genetic risk information. A major limitation of the latter study was recruitment of undergraduate students, their families and friends as participants. Many of the students required the data for their coursework, which suggests participation bias and conflict of interest may have influenced the results.

A recent study[62] investigating the hypothesised impact of genetic risk information for diabetes, heart disease, colon cancer and lung cancer found high levels of interest in genetic susceptibility testing regardless of degree of risk and disease type. Disease type did affect perceived psychosocial impact of genetic test result, with lower distress associated with hypothetical genetic risk for diabetes and heart disease, relative to hypothetical genetic risk for colon cancer and lung cancer. This can be explained by variations in perception of severity of disorder, with evidence among participants that diabetes and heart disease were perceived as being relatively less severe than lung and colon cancer. Diabetes and heart disease were also perceived to be more prevalent among first-degree relatives.

2.4.2 Impact of perceived genetic risk on attitudes of patients and relatives affected by psychiatric disorders

In the psychiatry setting, attitudes towards perceived genetic risk status have been investigated among patients,[64] or individuals with multiple family members, affected by bipolar disorder[65-69] psychotic disorders,[70] or schizophrenia.[22] These studies have been predominantly preliminary and/or qualitative studies involving people with multiple relatives affected by bipolar disorder[65-68] or schizophrenia[70, 71] and psychiatrists.[66, 67, 71] The majority of these studies reported high levels of interest of 83%,[71] 85%,[68, 70] 87%,[66] and 97%[67] in genetic susceptibility testing for susceptibility to bipolar disorder,[66-68] schizophrenia,[70, 71] or psychiatric disorders in general.[64, 72,73]

Meiser et al.[65] found that among 21 participants with a high familial density of bipolar disorder and among a total of 200 unaffected and affected individuals with multiple family members with bipolar disorder, the degree of interest in genetic susceptibility testing for risk of bipolar disorder depended on certainty of risk imparted by the test. The authors identified a range of perceived benefits and disadvantages of genetic testing for risk of bipolar disorder including facilitation of diagnosis; prevention and early intervention, particularly in adolescents; facilitation of protective health behaviours; improved treatment by providing a basis for matching medications to specific mutations (pharmacogenetics); and assistance with reproductive decisions.[65] Trippitelli et al.[68] found 'preventive treatment' was the greatest benefit cited among 90 individuals with bipolar disorder recruited from a genetic study and a bipolar disorder support group. Participants showed low concern about possible implications of knowing one's genetic information, but when prompted, ranked discrimination by one's insurance company as the greatest negative implication.

Most previous studies evaluating attitudes towards genetic susceptibility testing for bipolar disorder risk have found support for providing genetic tests for risk of bipolar disorder to children,[66-68] especially if preventive medication was available,[67] but indicated ambivalence about or little support for prenatal genetic testing.[66,68, 64, 73] Trippitelli et al.[68] found little support for terminating a pregnancy on the basis of a fetus having an increased risk for bipolar disorder, while Smith et al.[67] found that the degree of severity of the course of bipolar disorder, if it could be known, corresponded with the degree of willingness to terminate a pregnancy. A recent study involving individuals with self reported bipolar disorder or siblings of such an individual found psychiatric history had little impact on reproductive choices.[74] Meiser et al.[65] found hypothetical genetic risk status for bipolar disorder had mixed impact on child-bearing decisions. When examining reproductive these issues quantitatively among 95 unaffected and 105 affected participants with either bipolar disorder, schizo-affective disorder – manic type, or recurrent major depressive disorder, Meiser et al.[75] found that 35% of participants

were 'not at all willing to have children' or 'less willing to have children' as a result of having a strong family history of bipolar disorder.

These results are consistent with earlier findings involving major depressive disorder, bipolar disorder and schizophrenia. Illes et al.[72] showed that 23% and 56% of 316 patients with schizophrenia and/or an affective disorder unselected for family history reported that they would not have children in case of an increased genetic risk for depression and/or schizophrenia respectively. Austin et al.[70] found unaffected individuals who overestimated risk of developing a psychotic disorder based on having a relative with psychosis, showed greatest support for genetic testing including prenatal genetic testing, and favoured having few or no children. DeLisi et al.[71] found that more than half of unaffected individuals with at least two siblings with diagnosed schizophrenia or schizoaffective disorder supported prenatal testing of one's own unborn child. Compared to the findings of Mesier et al.[65] these findings suggest unaffected relatives perceive schizophrenia and other psychotic disorders as more severe than bipolar disorder and would be more likely to support use of genetic risk information to prevent the birth of a child at increased risk of schizophrenia or other psychotic disorders. A high likelihood of support for genetic testing was evident for bipolar disorder when the disorder was perceived as severe but not when perceived as mild.[67]

Previous studies about attitudes towards genetic susceptibility testing for risk of schizophrenia or psychotic disorders have been small and suffered methodological problems. Austin et al.[70] recruited participants from a psychosis support/information website, resulting in a very low response rate with approximately 1.5% of all website visitors completing the survey. DeLisi et al.[71] recruited participants via questionnaires mailed to unaffected family members who had previously participated in genetic studies, with a low response rate of 48%. While the findings contribute to valuable discourse to the debate about the use of genetic risk information in psychiatry, larger studies are needed to determine the extent of these findings in a more representative sample.

The majority of the attitude studies about genetic testing for risk of bipolar disorder recruited participants from molecular genetics studies or support groups (e.g.[65-68]), which suggests participants were already receptive towards genetic testing and could account for the high rates of interest in genetic testing. In one study,[68] deterministic framing of genetic risk information to participants as a "gene for bipolar disorder" falsely suggested bipolar disorder had a fully penetrant monogenic aetiology, which could have led to participants making genetic testing and child-bearing decisions based on greater certainty of risk than is truly the case for bipolar disorder.

Despite a likely positive bias of participants towards genetic susceptibility testing given prior enrolment in molecular genetic studies, these attitude studies have revealed a valuable range of beliefs about perceived risks and benefits of such tests. The findings suggest that participants believe perceived benefits of genetic susceptibility testing outweigh perceived limitations. These views might not be generalisable to other families with affected members, given the small sample of family members in each study, but it does provide a snapshot of attitudes in a population that will potentially be most affected by future genetic testing for bipolar disorder.

Attitudes towards use of genetic testing for bipolar disorder and schizophrenia and other psychotic disorders appear to predominantly hinge on the degree of certainty of risk and potential severity of the course of a psychiatric illness, neither of which can be determined by genetic information. These studies raise further questions about future use of genetic testing in psychiatry, should it become available. Ethical issues surrounding reproductive decisions, prenatal testing and testing children need addressing, together with issues about stigma, discrimination and the right to know or not know one's genetic information. These issues now require further qualitative investigation followed by quantitative studies using large national population samples. Given the high prevalence of major depressive disorder, and genetic studies showing promising allelic associations with major depressive disorder,[5] it is surprising that attitudes towards genetic susceptibility

testing for depression risk have not been investigated prior to the commencement of the research undertaken as part of this thesis.

2.4.3   Impact of disclosure of genetic test result

There is a growing body of literature on the psychosocial impact of genetic test result disclosure for adult-onset disorders. This includes studies on the impact of genetic testing for rare classical Mendelian disorders, such as Huntington disease,[55] familial cancers,[33, 56] early-onset familial Alzheimer disease,[76] hereditary haemochromatosis, polycystic kidney disease, hereditary muscular dystrophies and familial hypercholesteraemia.[55] The impact of test result disclosure for genetic variants with relatively low penetrance, for example, cancer susceptibility has also been well studied,[77] and one study has evaluated this issue for depression risk.[78] One of the most robustly replicated associations for a risk factor allele is the association between the apolipoprotein E (*APOE ε4*) polymorphism on chromosome 19 and Alzheimer disease in Caucasian populations.[79, 80,81] While strong interest in genetic susceptibility testing among first degree relatives has been reported,[82, 83] few studies have investigated the impact of *APOE ε4* genotype disclosure. The Risk Evaluation and Education for Alzheimer's (REVEAL) study,[79, 84] a multicentre randomised control trial involving 162 adults with a parent with Alzheimer disease, found disclosure of the presence the *APOE ε4* allele did not encourage recipients to believe they had a greater risk for Alzheimer disease beyond lifetime risk estimates. In contrast, those without the *APOE ε4* allele believed that their risk for Alzheimer disease was lower than estimated lifetime risk. However, rather than encourage false reassurance, the latter group reported an understanding that their family history still placed them at higher risk than the population. The authors concluded that their findings matched other studies investigating the impact of genotype disclosure, although the small sample in the REVEAL study may limit its generalisation to other populations and disease genotyping.

The REVEAL study also reported that there were no significant differences in anxiety, depression or test-related distress between groups who received or did not

receive their *APOE* genotype test result, whether or not they had the *APOE ε4* allele.[80] A subset without the *APOE ε4* allele showed a significantly lower level of test-related distress than did those with the higher risk allele. Since the level of emotional distress prior to test result disclosure increased the likelihood of post test distress, the findings stress the importance of providing *APOE* genotyping with genetic counselling.

A report involving a subset of 66 REVEAL participants compared the effect of adding genotype disclosure to family history and lifetime risk estimates to risk assessment for Alzheimer disease to risk assessment using family history and lifetime risk estimates alone.[57] The group receiving risk information based on family history and lifetime risk estimates alone reported the information had little impact, while the group receiving additional genotype disclosure, reported lower perceived risk for Alzheimer disease, less anxiety and greater benefit from the risk assessment. The findings appear to be influenced by relief among those learning that they did not carry the *APOE ε4* allele. Socio-demographic homogeneity of the participants and small sample size limited extrapolation of the findings to the broader population.

Wilhelm et al.[78] provide the only known data on the impact of disclosure of a genotype result for a mood disorder, using *5-HTTLPR* genotyping, which was then thought to be a marker of depression risk in consort with stressful life events. The original study followed a cohort of 128 teachers for 25 years documenting stressful life events and depressive episodes. Sixty-six per cent of the original participants elected to learn their genotype result, which is consistent with the high interest in genetic testing seen in previous studies. The authors found no marked distress associated with the receipt of test results in all genotype groups, although the 'higher risk' *s/s* group showed higher distress than the other two groups. Perceived benefits and limitations of 'depression risk' genetic testing reported by participants were also consistent with previous studies. The highest ranked perceived benefit was that genetic testing allowed for earlier intervention and provided potential to prevent the onset of depression. The highest ranked perceived limitation was that

serotonin transporter genotyping could lead to discrimination by insurance companies and employers.

Prior to disclosure of genotype results, and after controlling for a history of major depressive disorder, the *s/s* genotype group showed significantly higher estimates of personal risk of future episodes of depression than each of the other study groups, including the *s/l* and *l/l* genotype groups as well as people declining to receive results. The authors noted that participants appeared to understand that the genotype conferred susceptibility to depression rather than having a direct causal effect. Until 2009, the *5-HTTLPR* s/s polymorphism provided the strongest evidence of a genotypic association with depression risk. Lack of comparative studies assessing impact of genetic test result disclosure for risk of major depressive disorder limits the determination of the significance of these findings.

2.4.4   Conclusions

The evidence thus far shows that disclosure of genetic test results indicating a higher risk allele appears to not cause undue distress to those who have the allele, and may offer relief to those who do not, as is the case of genotype disclosure for Alzheimer disease.

Until more genetic associations with multifactorial disease are robustly replicated and studies are carried out assessing participant response to genotype, the impact of disclosure of genotype status for risk of multifactorial disorders cannot be fully understood. The REVEAL study has provided a preliminary basis for understanding the impact of the presence or absence of risk alleles, but further investigation is required to understand how genotyping impacts on recipients' perception of the *magnitude* of risk and how recipients interpret numerical risk estimates. Since perception of the impact of increased genetic risk, which is related to perceived severity and heritability, is shown to vary between disorders, including between psychiatric disorders, studies focused on major depressive disorder are required if the psychosocial impacts of genetic tests for depression risk alleles are to be determined.

2.5   Impact of genetic risk information on health behaviour

How individuals respond to genetic risk is especially complex when penetrance and predictive power of genotype is uncertain. The issue is further complicated by knowledge that a genetic component only represents part of the risk for multifactorial disease and appropriate behavioural responses to environmental risk factors are also required to make health behavioural interventions effective.

Health interventions based on genetic risk information considered most likely to work are those that are based on theories of behavioural change.[85] Two of the most salient models that have been proposed are Roger's Protection Motivation Theory,[86] based on fear of consequences of disease as a motivator of behavioural change, and Leventhal's Common Sense Model of Self-regulation,[87] which proposes that behavioural change depends upon causes attributed to disease and perceptions of the ability to modify those causes.

Rogers' Protection Motivation Theory posits that health-protective change depends on the relationship between fear and perceived magnitude of noxiousness of the disease, the probability that the disease will develop, and the perceived protection afforded by the health behaviour. Rogers noted that differences in magnitude of the seriousness of different health risks, for example, tooth decay versus lung cancer, posed a problem when comparing studies that examined behavioural response to disease and proposed a continuum of motivation to change behaviour to assist comparison and interpretation between studies.

A meta-analysis[88] of studies that employed the Protection Motivation Theory in health education programs revealed that the provision of fear-arousing health information was more successful in facilitating behavioural change than the provision of balanced factual information alone. Studies reported that participants informed of a high risk for lung cancer were more likely to change their smoking habits than participants informed of a low risk. A major flaw of these studies was that the information provided was not based on actual risk. It is possible hypothetical risk would be less likely to induce the level of fear required to prompt

behavioural change. This is borne out by the findings of a more recent intervention study involving a hypothetical genetic predisposition to lung cancer as a result of smoking. The study found reported fear, perceived risk and depression failed to deter participants (who were established smokers) from smoking.[62] The hypothetical nature of the scenario could have tempered the impact of the risk information provided. Furthermore, perceptions of causes of lung cancer (e.g. perceived unmodifiable genetic causes versus perceived modifiable smoking behaviour), together with perceived disease severity and degree of individual risk also impact on motivation to change smoking behaviour. The highly addictive nature of nictotine may also play a role in a trade off between impact of information about cancer risk and motivation for behavioural change.

Perceptions of causes of a disease and thus how readily health risks for that disease may be perceievd as modifiable is the basis for Leventhal's Common Sense Model of Self-Regulation,[87] which is commonly used as a theoretical framework to guide research into the efficacy of molecular-based preventive health interventions.[89, 90] Leventhal hypothesised that motivation to engage in health behaviours that reduce the risk for a disease depends on the causal attribution of risk and whether risk is perceived as less preventable (genetic causal attributions) or controllable (environmental causal attributions).[87] Genetic attributions may be perceived as deterministic (absolute causality) or probabilistic (increased risk). It has been argued that genetic susceptibility test results indicating low risk for a disorder should provide relief and reassurance, while test results indicating increased risk are expected to prompt health protective behaviours.[91] There is some evidence that, rather than facilitating protective behavioural change, genetic susceptibility that is perceived as immutable could prompt fatalistic attitudes, thus inhibiting willingness to engage in protective health behaviours.[60, 63, 85, 92, 93] It should also be noted that the provision of genetic risk information about a disease may itself influence causes attributed to that disease,[60] which may in turn impact on receptivity to genetic testing and molecular-based preventive health interventions. However, compared to Protection Motivation Theory, which depends upon an immediate or short-term fear response to disease risk, Leventhal's Common Sense

Model of Self-Regulation is likely to have greater utility in predicting future behaviour.

Previous studies have focused on behavioural change following predictive genetic testing for Mendelian-type disorders such as hereditary breast, ovarian, and/or colorectal cancer.[94, 95] An observational study of BRCA1 carriers in racial and ethnic subgroups showed a preference for surveillance rather than preventive surgery or chemoprevention.[94] A qualitative study of the consequences of increased hereditary risk for breast cancer in women with a family history of breast cancer found increased psychological distress in a minority of participants; perceived control over one's increased risk by adopting healthy lifestyle strategies such as a healthy diet, exercise, stopping smoking, use of natural remedies and stress management; and a demand for further information about breast cancer.[95] Both studies suffered from small sample sizes, short-term duration, and the latter had low response and participation rates, limiting generalisation.

A review paper found consistency in reporting that genetic testing is associated with increased adherence to surveillance and screening practices in cancer syndromes and that genetic testing for breast, ovarian or familial colon cancer was associated with greater use of risk-reducing surgeries.[96] Comparisons with such studies to determine health behaviour outcomes from genetic susceptibility testing for psychiatric disorders or other common complex disorders are limited, because gene mutations for familial cancers are highly penetrant and specific well-known guidelines for screening, surveillance, and surgery have been developed.

Research to assess the impact of genetic risk information on health-related behaviours involving gene-disease associations with uncertain penetrance has predominantly included heart disease,[92] familial hypercholesterolaemia (FH),[92, 93] nicotine dependence,[63] and Alzheimer disease.[79] Few studies have examined the extent to which genetic risk status for psychiatric disorders promotes changes in health behaviours.

A study examining response to predictive genetic testing for the FH mutation showed that participants with the high-risk mutation more strongly believed that a biological-based intervention such as cholesterol-lowering medication would be most effective in reducing their cholesterol level and believed less strongly that behavioural change, such as altering diet, would be effective.[93] Similar results were obtained in a small qualitative study on the impact of neonatal genetic screening for FH, in which parents who perceived the condition as dietary rather than genetic in origin, viewed the condition controllable by altering neonatal diet.[92]

These studies show that genetic risk information may influence perceptions of control over disease risk leading to selection of biological-based interventions when risk was perceived as genetic in origin and less preventable, or behavioural-based interventions when risk was perceived as environmental in origin and therefore more controllable, consistent with Leventhal's Common Sense Model of Self-Regulation.[87] They provide evidence that the provision of genetic risk information to people with a familial predisposition appears not to lead to a sense of fatalism but instead prompt perceptions that risk might be modifiable. This finding is contrary to perceptions reported in general populations, where fatalism in relation to genetic disorders is reported to be common.[97]

A larger British study of 269 smokers found that hypothetical increased genetic risk for nicotine dependence increased a preference for pharmacological methods to stop smoking over willpower.[63] While this result may have been confounded by the fact that the two outcomes, pharmacological strategy versus willpower, were not independent since participants were asked to select three cessation methods out of six, it suggests genetic risk information could undermine preventive interventions that are non-biological.

While there is strong evidence that genetic risk information impacts on perception of disease, which in turn has implications for health behaviour,[60] it has been argued that provision of information about individual genetic risk alone may not be sufficient to change health-related behaviour.[85, 98, 99] It will be necessary to evaluate the synergistic effects of individual genotype with personal and family

history of psychiatric disorders, and lifestyle and environmental factors that regulate gene expression.[11] Furthermore, targeted education should accompany such interventions to enhance understanding about factors that increase risk for depression among high risk groups and precipitate behavioural change. This strategy was successful in the San Francisco Mood Survey Project in significantly reducing depression levels among people who had been previously symptomatic.[100] Participants watched a television mini-series designed to teach social and coping skills using techniques from cognitive behavioural therapy. The study reported significant improvements in mood among the intervention group and significant changes in three behaviours including 'thinking about how to keep from getting depressed; 'telling oneself to stop having negative thoughts' and 'relaxation'. Although the scope of the study was limited by its short duration, low participation rate and low number of individuals who watched some of the television segments, it suggests that a community based preventive mental health intervention disseminated via the media could have positive short term effects.

Despite the recent uncertainty over a G x E association for major depressive disorder,[23, 24, 26] the G x E model could be used as a theoretical framework to design preventive interventions. For example, such an intervention could target asymptomatic individuals with a family history of major depressive disorder and identify individuals with the *s/s* genotype, which is reported to be associated with emotional (less adaptive) response to stress.[101] Such interventions could aim to facilitate more adaptive problem-solving coping strategies among this target group, thereby potentially reducing their risk for depression. Actual genotyping would depend on confirmation of effect size of a particular marker or markers from GWA studies and meta-analyses, and confirmation of clinical utility from the findings of future behavioural studies that evaluate response to genetic information. It should be noted that the study upon which this proposed intervention model is based involved a small sample with ethnic and socio-economic homogeneity.[101]

2.5.1 Conclusions

This review has identified a clear gap in the literature about how genetic risk information about psychiatric disorders, particularly major depressive disorder, might influence motivation to engage in protective health behaviours. Although genotyping for psychiatric disorders is not clinically available at present, it is necessary to employ hypothetical scenarios and family history information to gauge the potential impact of such information on perceived health protective behaviours in research populations before such genotyping is made available.

There is not enough evidence thus far to support the notion that an unfavourable result from a genetic susceptibility test will prompt health protective behaviours. There is also a risk that a favourable (low-risk) results could cause individuals to neglect their health in the false belief that their 'good genes' will be protective. On both accounts, consumers of DTC genetic testing services are at risk of making poor health decisions, possibly with inadequate genetic counselling. Large studies are required to determine the impact of genotyping on health behaviours to inform future molecular-based preventive health interventions and policy regarding DTC genetic testing.

2.6 Discrimination, ethical and privacy issues

A long-standing issue surrounding genetic susceptibility testing is its potential to lead to misuse of genetic risk information, through employment and insurance discrimination or breach of privacy.[102] Genetic test results indicating probabilistic risk, which would be the case for psychiatric disorders, are especially problematic since an individual could be vulnerable to genetic discrimination based on a disorder that may never develop. Furthermore, false positive results could lead to discrimination where no known risk exists. Internationally, there have been moves to initiate recommendations for policy-makers to protect individuals against genetic discrimination.

2.6.1 Discrimination

United States

In the US, legislative activities have led to the Genetic Information Nondiscrimination Act of 2008, which is discussed in Chapter 2.10. Supporters of the Act argue that the legislation is necessary so that individuals may access genetic diagnostic tests without fear of personal genetic information being misused.[103] Critics claim that even with legislative protection, many individuals do not trust insurance companies and other institutions and may still fear genetic discrimination, which impacts on access to genetic tests for preventive health care.[103,104]

The Genetic Information Nondiscrimination act of 2008 does not apply to members of the US armed forces from long-standing discriminatory policies in the military regarding the use of genetic information. However, the passage of Genetic Information Nondiscrimination act has led to a shift in US Department of Defense policy for fair use of genetic information in the determination of benefits for servicemen and servicewomen leaving military service.[105]

Until 2008, the US Department of Defense only provided benefits to service personnel receiving a medical discharge for non-genetic diseases that occurred during active duty. If an active-duty service member developed a disease with a known genetic basis, the armed forces considered the genetic predisposition to disease to be equivalent to a disease existing prior to service and denied benefits. Rare exceptions were granted if it could be proven that the genetic disorder was aggravated by military service.

It is not clear how identification of genetic contributors to common complex diseases will affect the interpretation and imposition of military policies and it is not known how the military may use genetic information in the future as understanding of genetic science progresses.

The US Genetic Information Nondiscrimination Act is enforced via four Federal laws that govern the provision of health insurance in the US. The laws are

enforced by Federal agencies including the US Department of Health and Human Services, the US Department of Labor and the Equal Employment Opportunity Commission, with penalties for violations consistent with other laws. [105]

Europe

A case in point is the outcome of genetic non-discrimination legislation, introduced in 1990 in Belgium, the first European country to initiate regulation. Despite a national legal ban on the use of genetic information in insurance risk assessment and any circumstances where an applicant benefits from protection of privacy, medical advisors and underwriters could nevertheless use genetic test results or genetic information derived from medical records or insurance questionnaires.[103] It is thought this situation arose from a poor understanding of genetic risk information and confusion over what is legally recognised as 'genetic' and 'non-genetic' data.[106] The regulatory framework throughout the rest of Europe varies considerably. Austria, Denmark, Estonia, France, Luxembourg and Norway introduced legislation in the early 1990s that banned outright the use of genetic information in insurance underwriting, while other countries, including Sweden, Switzerland, Finland, Germany, the Netherlands and the UK, adopted the use of moratoria.[106]

For example, in the UK, a 5-year moratorium prohibits the use of genetic test results in assessing applications for life insurance policies up to a value of £500,000, and for critical illness, long-term care and income protection policies up to a value of £300,000. In some circumstances, the UK's Genetics and Insurance Committee may permit the use of genetic test results below these thresholds, for example, for Huntington disease. In Greece, which also lacks appropriate legislation, insurance companies have agreed to a voluntary code of conduct and do not ask for genetic testing prior to insuring patients. However, there is currently no legislation dealing specifically with the issue of genetic discrimination in life insurance in Iceland, Ireland, Italy, Portugal and Spain.[106] Although Iceland has presented a bill to parliament, without the enactment of legislation Icelandic individuals whose personal genetic information has been collected on the national genetic database are particularly vulnerable (as discussed in Chapter 2.6.3).

Only a few European countries, including Austria, Estonia and France, have adopted legislation which prohibits genetic testing by employers. In Switzerland and the Netherlands, genetic tests can only be used by employers where there is an unambiguous health requirement for the job, or where the protection of the employee's health in the workplace calls for such a test.[106] In the UK, where there is no legislative prohibition on the use of genetic information in employment, discrimination on the basis of an existing disability of genetic origin is prohibited by the Disability Discrimination Act 1995, but there is currently no specific legislation to prevent discrimination against asymptomatic employees who have accessed genetic susceptibility testing.[106]

Australia

In Australia, the insurance industry's peak body, Investment and Financial Services Association (IFSA) (www.ifsa.com.au) requires disclosure of genetic test results for risk assessment. The IFSA takes into account the benefits of special medical monitoring, early medical treatment, compliance with treatment and the likelihood of successful medical treatment when assessing overall risk, but does not distinguish between the results of presymptomatic testing for predicting adult-onset disorders and the results of genetic testing for estimating the *risk* of adult-onset disorders. Thus, the results of genetic susceptibility tests for multifactorial disorders may lead to denial of insurance, shorter periods of cover or higher premiums. Generation of genetic risk information before genetic anti-discrimination legislation has been developed has major implications. The significance of this has increased since the proliferation of DTC genetic tests for a broad range of multifactorial disorders. Individuals who purchase such tests without informed consideration, especially tests that provide little meaningful information, may inadvertently prejudice their insurance and employment options. This is has become a pertinent issue since an Australian insurance provider, NIB (www.navigenics.com/partners/nib_customers), began offering its customers half-price genetic testing this year through Navigenics (as discussed in Chapter 2.4). In Australia, the results of genetic tests do not currently affect applications for health insurance, which is community rated, but NIB, which also sells life insurance, fails

to mention in its marketing materials the potential for discrimination when applying for life insurance or income protection insurance.

There is an imperative for anti-discrimination legislation in Australia, highlighted by the findings of a study in 2009 which identified the first cases of verified genetic discrimination on the basis of the results of genetic susceptibility tests.[107] The genetic tests involved highly penetrant mutations for familial cancer, Huntington disease, hereditary haemochromatosis and polycystic kidney disease rather than variants associated with psychiatric disorders. The discrimination included cases of access to life insurance, applications for worker's compensation and early release from prison and fear of discrimination can impact on access to genetic testing.

2.6.2   Ethical issues

Since genetic susceptibility testing may reveal probabilistic risk information about relatives of the individual tested, including any future children, test results raise confidentiality issues for the individual tested and ethical issues about relatives' right to know or right to not know their genetic risks. Genetic information that could affect relatives of the test recipient also raises conflicting ethical obligations for the health professional. Clinicians are not permitted to disclose a genetic test result to at-risk relatives without the patient's consent. Where non-disclosure of the test result poses a threat to the life of high-risk relatives, clinicians have a duty of care to disclose genetic information to such relatives at the expense of patient confidentiality. The implications for relatives are significant in the case of severe genetic disease, but for multifactorial disorders with probabilistic risk such as psychiatric disease, the ethical trade-off between patient confidentiality and relatives' perceived right-to-know their genetic risk is less clear.

Guidelines about disclosure of genetic information to family members for Mendelian genetic disorders, such as familial cancers, exist, but extrapolation to psychiatric disorders are limited because gene mutations for familial cancers, for example, are highly penetrant and screening and preventive treatments are available. Some argue that disclosure of genetic information to relatives is an

ethical duty, but problems arise when patients exercise their right to *not* know their genetic status, or if they do choose to know, to refuse to provide permission for disclosure to relatives.[108]

2.6.3 Privacy

The issue of privacy and control of one's own genetic information is highlighted by the example of Iceland's Health Sector Database, which holds health information and DNA samples for the whole population of Iceland (approximately 270,000 people). Under contract with the Icelandic government, the database was established in 1998 and was operated by the commercial Icelandic biopharmaceutical company, deCODE Genetics (www.decode.com) based in Reykjavik, which also provided international DTC genetic testing services. Under the 12-year license, drug companies could access the data for a fee, while academic researchers could have free access.[109] Controversy ensued surrounding issues of confidentiality, privacy and consent. Despite the company's assurances that individual identities would be protected by encrypting data and personal identifiers,[110] doubts have hung over the security of the data.[111] Opponents considered the database to be a government intrusion into the confidential relationship between patients and the doctors to whom they gave a DNA sample.[112] Controversy escalated when a venture capital group, Saga Investments, bought deCODE Genetics in 2009 after the company filed for bankruptcy, including its deCODEme personalised genetic testing service. Since the Iceland Health Sector Database operated on the premise of 'presumed consent' with an opt-out clause, the new owner was not obliged to recontact individuals for further consent to use the database for commercial research purposes. deCODE Genetics defines 'presumed consent' as "consent of society to the use of health care information according to the norms of society."[109] Presumed consent fails to provide for the right of an individual to have control over future use of their DNA.[113] Thus genetic information on the Iceland Health Sector Database and DNA provided by thousands of people who paid deCODE Genetics for DTC genetic tests can be sold to researchers and pharmaceutical companies for the

development of diagnostic tests and drugs without informed consent[114] or assurance of privacy.

Burke et al (2001) proposed that genetic tests should be categorised according to clinical validity and availability of effective treatment to assist the development of a framework to guide the ethical, legal, and social implications surrounding test decisions.[115] Genetic science has advanced considerably since the development of this model. Since geneting testing for mutlifactorial disorders has become a major issue of ethical and social concern, especially since advent of direct-to consumer genetic tests, it is now especially important that an ethical framework takes into account that the risks generated by genetic information do not apply equally to all types of genetic tests.

If and when new genetic tests emerge for multifactorial disorders, it remains relevant to commence an ethical, legal, and social implication analysis with consideration of the clinical validity of the test and the effectiveness and availability of treatment for people receiving a test result indicating higher risk variants. Ethical analysis may also enable anticipation of the issues raised by different genetic tests for complex multifacorial disorders, explain why some genetic tests generate serious and legitimate concerns and point to further research that will be urgently required.[115] Application of an ethical framework that categorises genetic tests according to clinical validity and treatment options to genetic tests that have limited predictive value, such as hypothetical genetic tests for psychiatric disorders, may have limited value. If developed, the medical and social outcomes of such genetic tests should be carefully considered to provide clinicians and policy-makers with the information needed to determine appropriate test use.

2.6.4   Conclusions

Recent evidence of genetic discrimination increases the impetus for policies and guidelines to be developed and implemented to ensure appropriate use of future genetic test results in psychiatry. International variation in legal protection and

scope for genetic discrimination despite the existence of legislation may undermine public confidence in genetic testing and preclude individuals from obtaining a genetic test who might benefit from doing so. Fear of discrimination may vary according to disease-type, which suggests perceived discrimination resulting from psychiatric genetic tests may differ from perceptions of discrimination resulting from test results for other medical conditions. The example of the Iceland Health Sector Database illustrates the implications of a commercially run national DNA health database and DTC genetic tests where one cannot be certain of how personal genetic information provided for medical reasons might be used in the longer term. Before genetic susceptibility tests can be developed for psychiatric disorders in the clinical setting, it will be necessary to research perceived genetic discrimination and privacy issues surrounding genetic testing for risk of psychiatric disorders.

2.7 Stigma

Mental illness stigma has been described as negative labelling, stereotyping, social distancing, emotional reactivity, status loss and discrimination.[116] According to attribution theory, defining an underlying biological basis for psychiatric disorders is likely to decrease the stigma associated with mental illnesses and resulting discrimination.[65] Specifically this theory states that a genetic explanation (an uncontrollable biological cause) will decrease stigma by shifting responsibility away from self to one's biology, thus reducing blame and increasing sympathy.[117-120] The alternate theory is 'genetic essentialism', which centres on the belief that genes form the basis of human identity and that a genetic explanation could increase stigma by increasing perceptions of "differentness" thereby increasing "social distance".[121] Phelan[122] took this hypothesis further by suggesting that evidence of genetic origins through genetic testing could make the person with a mental illness seem "defective" or "physically distinct" or "almost a different species."

Studies supporting attribution theory involving parents of a child with schizophrenia[123] or bipolar disorder,[65] claim attribution to a proven genetic component replaces prevailing beliefs about 'poor parenting' as a cause for mental illness. Thus such attributions can result in relief for parents, although parents may still face guilt at passing on a genetic predisposition.[119] Studies supporting genetic essentialism found that genetic attribution to mental illness increased perceived seriousness of such disorders, decreased the likelihood of social acceptance and thus increased stigma.[75, 117, 124] Studies have also found evidence of stigma by association, involving perceptions that children and siblings of individuals with a mental illness will also develop the illness, resulting in social distancing and consequently reduced social opportunities.[117]

The majority of studies investigating the relationship between genes, mental illness and stigma are small and preliminary. However, a large Australian population survey involving 2031 people examined whether perceptions of genetics as a cause of mental illness varied between mental illnesses.[125] The study identified stronger recognition of genetics as a causal attribution for schizophrenia than for depression, with a large minority perceiving no role for genetic factors in depression.[125] This is consistent with a review paper that suggested knowledge of a genetic predisposition for more serious psychiatric disorders, such as psychotic depression and schizophrenia, was likely to invoke higher levels of stigma based on perceptions that such disorders have a greater genetic contribution, with few modifiable environmental risk factors, and posed a greater threat.[126] In contrast, the authors suggested knowledge of a genetic predisposition for depression and anxiety was likely to invoke lower levels of stigma based on perceptions that such disorders have a smaller genetic contribution, have modifiable environmental risk factors and pose a lower threat.[126] It could be surmised from these results that differences in genetic attributions between mental illnesses could drive differences in perceived stigma associated with these illnesses, depending on whether genetic essentialism or attribution theory is supported.

2.7.1   Conclusions

It is well established that mental illness is stigmatised but it is not known whether clinical use of genetic risk information in psychiatry would exacerbate or reduce stigma. Educational interventions using genetic risk information should take into account differences in causal attributions of mental illness as a driver of differences in perceived stigma. If genetic testing becomes available in psychiatry, impact of genetic test results on stigma, including self-stigma and stigma by association, should be considered since this may reduce willingness to engage in preventive interventions or seek medical help for future mental illness.

2.8   Media analysis

The news media play a significant role in influencing public understandings of the way psychiatric disorders develop and the contribution of molecular genetics to psychiatric illness.[127-131] They drive beliefs about causes of mental illness, accountability and mental health care solutions. Medical issues are placed higher on the public and political agenda when they receive intense coverage in the media.[132] Thus studying the media provides an insight into public thinking about a health issue with the goal of informing strategic communications which work to bring public discourse closer to current scientific thinking.

Medical genetics has received substantial coverage in the international media over the past few decades, with greater intensity of coverage appearing to coincide with announcements of discoveries of new susceptibility genes.[128] Media discourse about genetics and mental illness has been negligible.[133] One of the largest gaps in the literature regarding mental illness and the mass media is empirical evidence that links the mass media with understanding, attitudes and behaviours related to genetic advances in psychiatry.[133] For the media to be used effectively as a tool for social change, there is a call for better understanding of how media messages about genetics and mental illness are constructed, developed and conveyed.[134]

2.8.1   Frame analysis

One approach to analysing the media is frame analysis. Entman (2003) suggests that the framing of an issue heavily influences how the audience responds to that issue.[135] Journalists, editors and scientists have the opportunity to frame medical news and thus influence public and political perception of the importance of particular issues. Journalists do this by employing news frames, which give particular meanings to a story. Furthermore, journalists influence the news angle through type of 'expert' interviewed and quotes selected. Editors and sub-editors influence the news agenda through selection of headlines and position of the news item in the publication. Scientists may also contribute to news framing by pushing particular aspects of the findings of studies or not mentioning in a media interview, bias, limitations, the need for replication, or negative results. Thus, analysis of news frames about mental illness and genetics provides an opportunity to systematically determine how the media is likely to influence public discourse.[135]

Previous analyses of genetic news in the media identified genetic determinism,[136-138] genetic optimism[128] and genetic pessimism[128] as important agenda-setting frames. Although believed to be pervasive in the media,[136,139] genetic determinism is reported to have decreased in US news media between 1970 and 1994, with a significant decrease in the number of articles assigning genetic causes to mental and behavioural characteristics.[133]

Determinism frame

Genetic determinism has been defined as: "attribution of genetic causality in a totalistic and absolute fashion, especially where such a causal account does not accurately represent the probabilistic and multifactorial inputs into a particular characteristic of a biological entity."[139] Deterministic framing of media reports about the genetic component of multifactorial disorders may encourage beliefs that genetic factors confer total, not partial risk for disease. Reports from the early 1990s suggested that the media were dominated by an ever-increasing portrayal of deterministic representations of genetics.[136, 138]

It has been claimed that the use of metaphor, such as genes as a "blueprint", popular imagery and other literary devices[136] in the media encourage deterministic thinking and elicit a strong reaction to the possible consequences of biotechnology.[140] It has been argued that deterministic framing has the potential to overstate the role of genes in mental disorders and contribute to stigma associated with mental illness.[136, 141-143] One study, based on a sample of 972 American print media published during 1915-1995 found little empirical evidence for these assumptions both in the body of media articles and in headlines.[133, 139]

Optimism and pessimism frames

The genetic optimism frame promises genetic technologies will have a positive impact on individuals with a mental illness and may offer unrealistic hope about the efficacy and availability of molecular-based treatments,[128] while the genetic pessimism frame presents dystopian expectations. Genetic optimism is reported to be dominant in the US media, with optimistic news articles often published in response to announcements by the scientific community of newly discovered gene-disease associations.[128, 144, 145] Genetic optimism has been reported to persist in the media even after subsequent failure to replicate reported genetic-disease associations.[128]

2.8.2   Conclusions

Given the probabilistic nature of genetic risk in psychiatric disorders, media messages that fail to state uncertainties about risk could lead to inappropriate use of genetic tests with potentially adverse consequences.[146] It is especially imperative to be able to gauge public thinking since genetic tests for risk of psychiatric disorders have been available DTC via the Internet and biotechnology companies propose to launch further genetic susceptibility tests of this nature. It is expected that analysis of the Australian media will reveal how media framing of psychiatric genetics may potentially influence public debate and the impact of genetic testing on public mental health.

2.9 Public health implications of psychiatric genetic testing

Advances in genetic research have shifted the focus in psychiatry from treatment and management of symptoms towards prevention of relapse and prevention at an asymptomatic stage. Such an approach is currently limited because polymorphisms identified as being associated with major depressive disorder and bipolar disorder still require further replication, and clinical utility is still to be determined. Furthermore, genetic susceptibility tests would need to be designed based on multiple alleles since currently identified single polymorphisms only weakly predict risk. Since environmental risk factors such as stressful life events, difficult childhood and sexual abuse[65] are thought to provide a significant component of risk in interaction with genetic factors, genetic testing alone can only provide part of risk assessment.

The clinical value of a genetic test also depends on its sensitivity (how many cases of a disease a particular test can find), specificity (how accurately a test identifies particular alleles/mutations without giving false positive results), and positive and negative predictive values (the probability a test positive or negative is a true positive or true negative); the costs and benefits of interventions; and the availability of data linking specific variants to improved clinical outcomes. In addition, the lack of precision of diagnostic criteria for psychiatric disorders limits efficacy of use of genetic risk information. Even if genetic tests with adequate sensitivity and specificity could be developed and offered in a clinical setting, expenditure on population screening and counselling to identify small numbers at high risk is unlikely to be justified.[147]

A more cost-effective strategy would be to target individuals who have been identified as having a high genetic risk of developing depression and other psychiatric disorders, on the basis of family history. Both strategies raise questions for public health policy, especially justification of testing in the absence of effective preventive strategies. The Nuffield Council on Bioethics 1998 report[148] concluded that genetic tests would not be useful for diagnosing mental disorders with complex causes either prenatally or by population screening. One of the

report's main recommendations was that genetic susceptibility testing offering low predictive or diagnostic certainty should be discouraged unless there are clear medical benefits. In addition, screening high-risk families raises ethical issues about whether children and adolescents should be tested, particularly in relation to consent and stigma.[102] A related concern is that screening will unnecessarily raise anxiety about risk for a psychiatric disorder in individuals who are found to have susceptibility alleles, but who are at low risk of developing the disorder.

After implementation of psychiatric genetic testing services, geneticists, GPs and psychiatrists may experience pressure from patients for prenatal testing, genetic testing of children or potential adoptees, or pre-marital screening, with implications for provider education. Genetic counsellors note that genetic counselling for psychiatric disorders requires more specialised skills than dealing with many other kinds of common, complex disorders.[119] It will also be necessary to initiate consumer education campaigns about the genetics of complex diseases. Research is required on how to present such genetic information in ways that prompt behavioural change and do not undermine public health strategies.[147] Fatalistic attitudes in response to genetic risk information could impede the efficacy of potentially valuable genetic screening programs, necessitating genetic risk information to be presented in such a way to offset such attitudes. Common problems that will need to be addressed include popular misunderstandings of the consequences of carrying high-risk alleles and/or mutations and the impact of knowledge of one's genetic make-up on sense of identity.

Medical benefits of genetic screening for depression risk are currently unknown. A study that used the example of hereditary non-polyposis colorectal cancer (HNPCC) to examine risks and benefits of genetic testing found targeted screening of high risk individuals produced fewer risks and greater benefits than population screening.[149] The ability to extrapolate from adult-onset disorders that follow Mendelian inheritance and involve high-penetrance gene mutations such as HNPCC and/or hereditary breast cancer is limited because penetrance of the mutations involved and disease impacts differ greatly from psychiatric disorders. It is pertinent to note, however, that in cases where risk for colorectal cancer was

higher due to non-genetic factors, genetic testing had the potential to undermine the detection and reduction of other potentially important risk factors.[149]

One of the latest approaches to risk prediction and prevention for depression, known as PredictD, involved the development of a risk algorithm based on 39 recognised environmental and family risk factors for major depressive disorder.[150] The cross-national study tested the depression risk algorithm in 5216 general practice attendees in Europe and validated its use in 1732 general practice attendees in Chile. The authors found it provided useful thresholds of sensitivity and specificity and compared favourably with risk algorithms for prediction of cardiovascular events. It is yet to be determined how a risk algorithm could be best implemented in clinical practice. The authors propose that patients identified as being at risk on screening could be flagged on general practice computers to alert GPs during a consultation. This could lead to "watchful waiting" or active support, such as restarting treatment in patients with a history of depression. GP time constraints could limit its utility; however the authors have attempted to reduce workload of GPs using the tool by optimising its sensitivity and thereby minimising false positives.

PredictD does not include genetic risk information, but provides a public health model for risk prediction. Once the evidence base for genetic risk information about psychiatric disorders is robust, there is the potential for a predictive tool such as a risk algorithm to incorporate genetic factors in addition to established family history and environmental factors to create an efficacious instrument in the prediction, treatment and prevention of depression and other psychiatric disorders.

2.9.1   Conclusions

As the genetic testing industry gains momentum there is an imperative for the designing and planning of public health initiatives to determine the responsible use of genetic information in preventive health and mental health promotion. There are not enough specialists who can interpret genetic risk information and hence the

burden of managing future patients requesting and receiving personal psychiatric genetic information will fall to GPs.

At the individual level, where family history is strongly suggestive of a hereditary predisposition to depression, there may be clear benefits to offering genetic susceptibility testing if analytic and clinical validity of alleles and/or mutations tested are robust and where effective pre-symptomatic interventions are available. At the population level, the benefits of genetic susceptibility testing for future risk of a multifactorial disorder such as depression are less clear, since screening whole populations for a predisposition is not likely to be cost-effective.

Since DTC marketing of genetic tests means such tests could be purchased before public health protocols are in place, research is urgently required to determine attitudes towards genetic susceptibility testing for risk of depression, psychosocial impact of test results, and how such results could be used as part of preventive interventions. Furthermore, there is an imperative to train health professionals, including GPs, genetic counsellors, geneticists and to ensure that they are aware of the types of genetic tests offered DTC. They also need to be aware that some of these tests may lack analytic or clinical validity, so that they can counsel their patients about the potential value and limitations of DTC testing.

2.10 Governance

Genetic tests are considered *in vitro* diagnostic (IVD) medical devices under most national regulatory regimes. IVDs fall under the jurisdiction of the Food and Drug Administration (FDA), in the US, the *In Vitro* Diagnostic Medical Device Directive in the European Union and the Therapeutic Goods Administration (TGA) in Australia. Concern over the need to regulate laboratory-developed DTC genetic tests has led to government genetics advisory bodies around the world commencing expert consultations, public meetings and preparing proposed legislation to determine how genetic susceptibility testing should be regulated.[41,151]

North America

In 2002, the National Institutes of Health Task Force on Genetic Testing recommended that advertising or marketing of genetic susceptibility tests to the public should be discouraged. Similarly, a Canadian report[152] concluded that Canadian federal standards for approval of genetic testing should be carefully examined and monitored and that the federal government should ensure that DTC marketing of genetic testing should be restricted if not entirely prohibited for certain forms of testing.

In 2006, about half the states in America were permitted to market DTC genetic susceptibility tests.[153] The American Society of Human Genetics made recommendations in its 2007 report[153] that DTC companies should disclose sensitivity, specificity, and predictive value of the test; the strength of scientific evidence; all risks associated with testing, including psychological risks and risks to family members; certification status of the laboratory performing the genetic testing; privacy policy; and the need to maintain the privacy of all genetic information.

In June 2008, the California Department of Public Health issued cease and desist letters to 13 genetic testing companies ordering a ban on marketing genetic tests to Californian residents without a state license and the involvement of a state-licensed physician. These included the high profile companies 23andMe, Navigenics and deCODE Genetics. Navigenics subsequently employed a physician to order the tests and outsourced the laboratory work to co-collaborator, Affymetrix, a Federally-certified and California-licensed laboratory.[50]

The same year the US Government Accountability Office (GAO) launched an investigation into four biotechnology companies selling dietary-related genetic susceptibility tests. The investigators anonymously approached four online companies for testing services posing as 14 different would-be consumers with a variety of profiles such as age, weight, smoking and exercise habits. In reality, they sent samples of DNA provided from just two people – a 48-year-old man and a nine-month-old girl. The GAO's report[40] revealed that the companies, which

charged between US$89 and US$395 for the tests, provided similar results for each of their fictitious clients, together with vague and misleading advice. Post test follow up centred on 'tailored' nutritional supplements costing up to US$1,200 per year, which the authors stated were ordinary multivitamin tablets that could be bought from chemists for US$35 a year. The GAO investigation suggested that consumers could receive meaningless results from early vendors of DTC genetic testing services. This could have potentially serious consequences regarding DTC tests purported to predict risk of serious medical disorders such as heart disease, cancer and mental illness. As detailed in Chapter 2.4, an investigation involving genetic tests purported to reveal risk of breast cancer, colon cancer, prostate cancer, type 2 diabetes and heart attack, revealed large discrepancies in accuracy of risk prediction between two different companies.[49]

A recent initiative to encourage transparency among providers of genetic tests is the proposed launch of a voluntary genetic testing registry in 2011.[154] To be managed by the FDA or by the National Institutes of Health, the registry will provide an information resource for the public, including researchers, health care providers and patients, to enable sharing of test performance characteristics and availability and utility of particular DTC tests.

A major barrier to the development of genetic testing has been fear of discrimination based on genetic information, as described in Chapter 2.6.1. The US Genetic Information Nondiscrimination Act, signed into law in 2008, prohibits the improper use of genetic information in the underwriting of health insurance and employment, but does not include protection from genetic discrimination in life, disability, or long-term care insurance.[155] The Act specifically prohibits insurers from using a person's genetic information in determining insurance eligibility or insurance premiums, and requesting or requiring that a person undergo a genetic test; and prohibits employers from using a person's genetic information in making employment decisions such as hiring or firing, and requesting, requiring, or purchasing genetic information about persons or their family members.

Europe

In 2002, the UK Human Genetics Commission commenced a review of existing genetic tests available culminating in the *Genes Direct* report,[41] and *More Genes Direct*[156] which recommended stricter controls on DTC genetic testing. They concluded that most genetic tests that provided predictive health information, including new genetic susceptibility tests currently offered DTC, should be provided within the National Health Service and not be offered DTC. In 2006, governments of Switzerland and France introduced a universal ban on private genetic testing due to concerns about potential fraud or errors in the absence of proper regulation. Internationally, similar reports have been issued cautioning against use of DTC genetic testing.[41, 151] In 2008, the Council of Europe[157, 158] approved protocol concerning genetic testing for health purposes, including DTC genetic testing services. The Council of Europe recommended that genetic tests should meet accepted criteria of scientific and clinical validity; demonstrated clinical utility should be an essential criterion; appropriate genetic counselling should be available for genetic susceptibility tests; and persons providing genetic services must have appropriate qualifications. If all 46 European member states sign up to the protocol, DTC genetic testing could be prohibited in Europe.[157, 158]

Australia

In Australia, a two-year enquiry by the Australian Law Reform Commission (ALRC) and the Australian Health Ethics Committee (AHEC) of the National Health and Medical Research Council (NHMRC) led to publication of the 2003 consultation paper *Essentially Yours*,[151] which recommended that the supply and advertising of genetic tests DTC should be prohibited, except where specifically approved by the TGA.

Recently the TGA amended the Therapeutic Goods Act 1989 and other regulations to classify genetic tests as Class 3 IVDs (the second highest risk group) which the TGA defines as "devices that present a moderate public health risk, or a high individual risk." Furthermore, the regulation prohibits the supply of "self-testing IVDs to determine genetic traits" (DTC genetic tests).[35] In Australia, it is currently an offence to advertise a genetic IVD DTC on the Internet unless the device is

listed under the Therapeutic Goods Act, the Therapeutic Goods Regulations, and the Therapeutic Goods Advertising Code. However, the TGA is powerless to regulate advertisements when the Internet service provider is based overseas. In such cases, Australian jurisdiction is limited to liaising with consumer affairs bodies in the relevant country regarding DTC advertising material that is either posted on the Internet or mailed to Australian addresses. In addition, the TGA proposes that the Human Genetics Commission Australia develop a voluntary code of practice and other advice on DTC genetic testing. They recommend that such a code include minimum technical standards for companies supplying products and minimum ethical standards for laboratories supplying the testing service.

2.10.1 Conclusions

There is currently a dearth of scientific research to inform national and international policy about how laboratory-developed DTC genetic susceptibility testing should be regulated. Qualitative and quantitative community evaluation is required to assess interest in genetic susceptibility tests, especially tests marketed DTC, to inform policy. Once analytic and clinical validity and utility have been determined, professional guidelines are needed to inform policy to assist the transition of such tests from research to medical practice. It will be necessary to evaluate the psychosocial impact of such tests, including the capacity for discrimination regarding genetic test results. The further development of anti-discrimination legislation will be required as part of legislative protocols.

2.11 Summary of the literature review

Although genetic susceptibility testing for risk of psychiatric disorders is currently premature, DTC genetic tests are available from commercial laboratories, causing controversy in the psychiatric research community. Claims made by these companies are likely to be misleading and fail to adequately address limitations of the test result, such as weak effect of the allele tested and the potential for

discrimination. Evaluation of public health impacts of genetic susceptibility testing for psychiatric and other multifactorial disorders is predominantly based on hypothetical populations. The psychosocial impact of actual genotyping for risk of psychiatric disorders is not known as psychiatric genetic studies require replication. The research to date indicates high hypothetical interest in genetic testing for various multifactorial disorders. At commencement of the thesis, this question had not been researched for major depressive disorder.

Reports of genes that confer risk for psychiatric disorders appear frequently in the media, with anecdotal reports that such news may lead to increased demands on general practitioners for referrals for such tests. Over-emphasis on genetic attributions to psychiatric disorders in the news may lead to attitudes of genetic essentialism, with little known about subsequent impact on stigma associated with these disorders. Emphasis on genetic testing may mask the importance of risk for psychiatric disorders from non-genetic factors.

Research is clearly required to determine the psychosocial impact of genetic susceptibility testing for risk of psychiatric disorders. It is not known whether early intervention of healthy people based on a genetic susceptibility for a psychiatric disorder will reduce premature morbidity or mortality. For genetic susceptibility tests to have clinical value, data are required that link specific variants/mutations to improved clinical outcomes. Examples are seen for some common cancers, such as colorectal and breast cancer, where regular monitoring and early treatment have been shown to reduce mortality. However, comparisons are limited by differences in penetrance of susceptibility alleles and disease progression. Much needs to be learned about how to present and explain information about genetic risks for psychiatric disorders to achieve changes in health behaviour.

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3 STUDY 1A:

Public interest in genetic testing, including direct-to-consumer testing, for susceptibility to major depressive disorder: preliminary findings

3.1 Introduction

The identification of candidate genes thought to confer susceptibility to psychiatric illness, which manifest upon exposure to stressful life events, presents an opportunity to predict high-risk groups and reduce the burden of psychiatric disease through intervention strategies at a pre-symptomatic stage. Effective interventions that use genetic and environmental risk information will depend upon public understanding of the complexity of interactions between susceptibility genes of uncertain penetrance and environmental risk factors.

Risk prediction and preventive interventions, based prodromal features of schizophrenia, are already in place for youth at high risk of schizophrenia and other psychotic disorders. Studies demonstrate that early interventions in this group, such as pharmacotherapy and psychotherapy, may delay or even prevent progression to a diagnosable psychotic disorder such as schizophrenia.[1] Predictive genetic testing for markers of mental illness has thus far not been studied in prospective early intervention studies.

The recent proliferation of commercial start-up genetic testing companies marketing genetic susceptibility tests directly to consumers (DTC) has raised concerns about predictive validity and potential health impact of such tests.[2] Consumers may be at risk of selecting inappropriate tests, misinterpreting results and making harmful health decisions.[3] At the time of this study, there was an

upsurge of start up commercial biotechnology companies based predominantly in the US, UK and Iceland marketing DTC genetic susceptibility testing services. Some of these tests were available in clinical practice, but for some, including susceptibility genetic tests for psychiatric disorders, there has been little published data thus far to support clinical validity.[4]

As discussed in Chapter 2.2, a gene-disease susceptibility association that was reported by a large number of studies was an interaction between a functional polymorphism in the promoter region (*5-HTTLPR*) of the serotonin transporter gene (*SCL6A4*) and exposure to stressful life events in increasing the likelihood of major depressive disorder in non-clinical populations of adults,[5-8] adolescents[9] and children.[10] Studies suggested that individuals homozygous for the short allele (*s/s*) of the serotonin transporter gene-linked polymorphic region may be at increased risk for depression upon exposure to multiple stressful life events,[5-10] Debate regarding the validity of the association[11, 12] does not alter the approach taken in this study, although it would alter the specific genes to be tested. Critics argue that the meta-analyses[11, 12] had numerous inconsistencies[13,14] and should not be used to cast doubt on the importance of exploring G x E models in psychopathology.[13]

Psychosocial issues associated with genetic susceptibility testing for susceptibility to major depressive disorder are likely to be more complex than for Mendelian monogenic disorders because test results are not definitive. There will be implications for public policy and ethics with an impact on stigma[15-18] and concerns about potential misuse of genetic risk information, for example, through employment and insurance discrimination.[19] International government genetics advisory bodies have commenced expert consultations and public meetings to determine how genetic susceptibility testing should be regulated,[3, 20, 21] however, there is a dearth of scientific research to inform national and international policy.

Previous international scientific research in this area is predominantly limited to preliminary and/or qualitative studies on attitudes towards genetic risk information and genetic testing among members of families who have multiple relatives affected by bipolar disorder or schizophrenia.[15, 22-25] These studies have generally

found positive attitudes towards genetic susceptibility testing, and a recent quantitative study involving families with a high density of bipolar disorder showed that interest in testing increased with the certainty indicated by the test.[26]

3.2 Aims

No research to date has evaluated attitudes among the general population towards genetic susceptibility testing for depression risk and beliefs about the psychosocial implications. Since serotonin transporter genotyping was commercially available DTC in the US at the time of the present study, a hypothetical genetic susceptibility to major depressive disorder was used as an example of a genetic test to qualitatively evaluate public understanding of, and attitudes towards, risk prediction involving susceptibility genes for depression.

3.3 Materials and Methods

The results reported here were undertaken as part of a broader qualitative study, which also explored attitudes towards preventive mental health interventions based on genetic risk, which is reported in Chapter 4.[27]

As this is a relatively unexplored area of enquiry, a qualitative methodology was used. There has been an upsurge in interest in studies that examine attitudes, beliefs and experiences of people in connection to health care issues, and qualitative methodology has been increasingly recognised by evidence-based clinical researchers.[28]

3.3.1 Participants

A market research company was engaged to randomly recruit 10 participants each to four or more focus groups from their database of 10,000 members of the public

unselected for disease risk, ensuring an even mix of gender, age and socio-demographic backgrounds. Eligible participants included those 18 years or older, fluent in English, residing in the Sydney metropolitan area and have not participated in any research in the previous six months. Ethical approval for the study was provided by the relevant Institutional Review Board (Human Research Ethics Committee, University of New South Wales, Australia).

3.3.2   Focus group interviews

Participants were previously naïve to the focus group topic. They completed a short questionnaire that included items about age, sex, language spoken at home, occupation, and highest education level completed. Participants were asked to introduce themselves and indicate whether they had prior knowledge or experience of the subject of mental illness. They were not obliged to disclose personal or family history of mental illness.

The focus groups were conducted in accordance with widely accepted standards of focus group methodology.[29] They were facilitated by the author, a research health scientist and medical journalist, and observed by a research psychologist. Focus groups were recorded on digital video and the observer took written notes of the main themes discussed.

An interview guide was developed on the basis of a review of the relevant literature exploring the following topics: i) interest in genetic testing to determine susceptibility to major depressive disorder and ii) attitudes towards potential for social stigma, discrimination and issues of DNA privacy.

Depression risk genotyping was framed to participants as a 'genetic test to determine whether an individual has an increased risk for developing depression in the event of experiencing significant adversity.' A positive test result was framed to participants as a genetic result indicating an 'increased risk for depression'.

3.3.3   Analysis

The conceptual approaches of Patton[30] and Miles and Huberman[31] were used to guide the analysis. A detailed coding scheme was developed and transcripts were coded by the author. Ten percent of the transcripts were recoded by the research psychologist, to identify any discrepancies in interpretation of codes and refine the coding scheme. Discrepancies were discussed between coders to provide opportunities for developing further coding and consensus.[28] Coded transcripts were subsequently analysed for emergent themes with the assistance of the software package QSR N6, which facilitated comparisons between affected and unaffected participants as well as other aspects of the analysis.[31]

Corresponding to the qualitative nature of the data, focus group discussions were designed to identify the range of beliefs rather than extent to which participants held particular beliefs. However, to provide an indication of the extent of interest in genetic testing for susceptibility to depression, every participant was asked whether they would have genotyping for depression risk if it was available, and why, before and then again after discussion of perceived positive and negative psychosocial implications.

Participant quotations were coded according to lived experience (personal and familial implications) of mental illness: e.g. [A] reported personal or family history of major depressive disorder bipolar disorder or schizophrenia ('affected') or [U] no reported personal or family history of major depressive disorder, bipolar disorder or schizophrenia ('unaffected').

This highlighted any differences in attitudes towards genetic susceptibility testing among individuals for whom such testing would carry greater hereditary implications compared to those without a personal or family history. Interest in genetic testing was also coded: [YY], interested in having a genetic test for susceptibility to major depressive disorder both before and after considering implications; [YN], initially interested in having the genetic test but not after considering implications; [NN], not interested in having the genetic test both

before and after considering implications. Although the NY code was a theoretical possibility, it was not used because no participants fell into this category.

3.4 Results

3.4.1 Participation and demographics

Thirty-six people (18 female, 18 male) participated in a total of four focus groups held in four locations across Sydney. Recruitment was discontinued after the fourth focus group when informational redundancy was achieved, in accordance with standard qualitative methodology.[31] During focus group discussions, 14 participants spontaneously revealed a personal or family history of major depressive disorder, bipolar disorder or schizophrenia. Demographic characteristics of participants are shown in Table 1. The mean age was 41 (range 20-65 years).

Table 1. Demographic characteristics of sample.

Variable	'Affected' [A][1] (N=14)	'Unaffected' [U][2] (N =22)	Total sample[3] (N=36)
Sex	N	N	N
Male	5	13	18
Female	9	9	18
Age[3]			
18-29	2	5	7
30-39	6	6	12
40-49	1	3	4
50-59	4	2	6
60-69	1	5	6
Highest education level completed[3]			
Tertiary	9	9	18
High school	5	12	17

[1]Self reported personal or family history of major depressive disorder, bipolar disorder or schizophrenia. [2]No reported personal or family history of major depressive disorder, bipolar disorder or schizophrenia. [3]Missing value - participant declined age and education questions.

3.4.2   Interest in genetic susceptibility testing for depression risk

At the beginning of the discussion, the majority of participants (10 'affected', 14 'unaffected') indicated an interest in having a genetic test for susceptibility to a major depressive disorder if it was available. 'Unaffected' participants who said they would be interested in having genetic susceptibility testing were more hesitant and tended to attach conditions. Table 2 shows interest in depression risk genotyping before and after discussion of perceived positive and negative implications and reading of several media articles about various aspects of genes and mental illness. Participants who were initially interested in having depression risk genotyping but who changed their mind after the discussion, citied fear of

genetic discrimination and loss of privacy as major reasons. No participants changed their mind in the opposite direction.

Table 2. Interest in genetic susceptibility testing for depression risk

Interest	Participants		
	'Affected' [A][1]	**'Unaffected' [A][1]** (Unsure)[4]	**Total** (Unsure)[4]
Initially interested	10	14 (2)	24 (2)
No longer interested after discussion	4	5	9
Still interested after discussion	6	7 (4)	13 (4)

[4]Refers to participants who did not know if they would have such a test.

3.4.3 Perceived benefits of genetic susceptibility testing for depression risk

Benefits for families

'Affected' and 'unaffected' participants thought genetic testing for susceptibility to depression would be of greater benefit to those with a family history of the disorder.

> *"I couldn't imagine having the test unless there was somebody in the family with mental illness" [A/YY].*

Scope for early intervention

Participants with or without reported FH/PH thought depression risk genotyping would help them be ready to seek early help. One remarked: *"…forewarned is forearmed,"* which he believed would enable him to *"…deal with it should it arise"* [U/YY].

Another said:

> *"…I've seen my mum live through it, I think it's so much better to know straight out, start as soon as you can with whatever help you can get." [A/YY]*

One participant suggested depression risk genotyping could be a useful part of a general health check-up [A/YY]. One participant said knowledge of one's genetic risk could help people put techniques in place that might minimise or prevent the development or severity of depression.

Reduce social stigma

Several participants with reported FH/PH thought evidence of a genetic component would help validate depression and other mental illnesses as physical illnesses, which might decrease social stigma. One suggested this would lead to improved government funding for mental health research. Another disagreed with genetic testing for susceptibility to depression because "*the test is not definitive*", and "*no prevention is available.*"

Conditions attached to interest in genetic susceptibility testing

Conditions set by participants who did not report FH/PH interested in having depression risk genotyping included: "*if it ran in the family;*" [U/NN], "*if I needed it,*" [U/YY], "*if the doctor referred me,*" [U/YY]. One participant saw little point in having a genetic susceptibility test without availability of related interventions:

> "*You'd just wait for the signs of symptoms to come. Nothing is going to change; you don't start taking something just because there's a possibility you might [develop depression].*" [U/NN].

3.4.4   Perceived disadvantages of genetic susceptibility testing for depression risk

Fear of loss of privacy

While most participants said they trusted a genetic test result would remain private and confidential if obtained through the public health system, some participants were worried that privacy could not be guaranteed. One participant cited this as the reason why she would not have depression risk genotyping:

> *"...if [the test result] fell into the wrong hands or …you know we just*
> *live in such a fish bowl these days and no, couldn't bear the thought*
> *of it." [U/NN].*

Risk of discrimination

Many participants were concerned having depression risk genotyping could lead to discrimination by insurance companies and employers; which influenced several participants who did not report FH/PH against having a genetic susceptibility test, and caused another to change her mind:

> *"I know that if I had a test well it probably would come back positive.*
> *And if found that out and I couldn't get insurance well then I'd say*
> *no to a test." [A/YN].*

Risk of fatalistic thinking

Some participants thought they might develop fatalistic thinking if they were found to have an increased risk for depression:

> *"…once you find out…that you are in this predisposition it might*
> *send you over the mark …you'd be worrying the whole time - that's*
> *going to cause it." [A/YN].*

One participant viewed having the s/s variant as definitive with negative consequences:

> *"I mean you might be okay and then it comes back that you're*
> *depressed or you've got bipolar [disorder] and then you go and neck*
> *yourself." [U/YN].*

One participant disagreed with the fatalistic view, and emphasised the importance of awareness:

"I'd be worried if I wasn't aware…if it's 80% risk or something like
that at least I know, I'm aware that this could happen. I'm not going
to treat it as if it is happening." [A/YY].

Increase social stigma

Several participants (both those reporting and not reporting FH/PH) anticipated that genetic testing for predisposition to depression would not reduce social stigma attached to the disorder but could increase it:

"Whilst I see that [genetic susceptibility testing] might be valuable to
helping a person… I think social implications, social stigma is the
major problem." [A/YY].

3.4.5   Attitudes towards DTC genetic susceptibility testing marketed via the Internet

Participants were told that DTC genetic testing to determine predisposition to depression involved registering online and sending a saliva sample or cheek swab to an overseas genetic testing laboratory in a DNA test kit provided. All 26 participants who responded to this issue were unanimously against accessing DTC genetic susceptibility testing from biotechnology companies. Objections included concern about credibility of DTC genetic testing services, especially if obtained via the Internet, worry about security of DNA sample and privacy of genetic risk information, and lack of confidence in non face-to-face genetic counselling.

3.5 Discussion

3.5.1 Interest in genetic susceptibility testing for depression risk.

This study found positive attitudes towards genetic susceptibility testing associated with susceptibility to major depressive disorder if it were to become available, which supports previous findings for bipolar disorder or schizophrenia.[15, 18, 25, 26, 32] The results suggest having a personal or family experience of major depressive disorder, bipolar disorder or schizophrenia may be strong predictors of uptake of genetic susceptibility testing for mental disorders. Since the national estimated lifetime risk of mental illness is estimated to be 20-25%,[33] it is expected that a proportion of a population sample would report personal or family experience of depression or other mental disorders.

Perceived discrimination by insurers or employers and perceived risks to security of genetic information appeared to moderate interest in genetic susceptibility testing among both affected (having a personal or family history of a mental disorder) and unaffected individuals. Similar concerns were described in a study of attitudes towards genetic testing for susceptibility to schizophrenia.[25]

The majority of participants who were interested in having the hypothetical test said they would still have it despite the result offering a probabilistic rather than a definitive risk. These findings support a previous study of families with a high density of bipolar disorder, despite a comparably higher degree of perceived disadvantages of a probabilistic risk versus certainty of risk identified in the latter study.[15] It could be that members of families with a high frequency of bipolar disorder perceive uncertain risk to exert a greater burden than do affected or unaffected members of the public.

The majority of unaffected participants who were interested in having a hypothetical genetic test for susceptibility to depression tended to cite conditions under which they would have the test, while affected participants did not. This

suggests having a personal or family experience of a mental illness may engender a greater amenability towards depression risk genotyping. These attitudes may be influenced by naivety about low predictive power of such tests and low risk rates for close family members. Potential differences in attitude and approach to hypothetical genetic susceptibility testing between individuals reporting and not reporting a personal or family history of major depressive disorder should be considered when planning molecular-based preventive mental health interventions and public education about genetic testing for susceptibility to a psychiatric disorder. Further studies are required to find out whether these trends are borne out in larger non-clinical samples.

3.5.2 Interest in direct-to-consumer genetic susceptibility testing

No known previous studies have evaluated public interest in the emerging area of DTC genetic susceptibility testing. While unanimous opposition to DTC genetic susceptibility testing for depression risk alleles suggested low potential uptake of commercial genetic testing, minor interest was restored if protection from discrimination and DNA misuse could be guaranteed. Participants' trust in the public health system as a potential provider of genetic susceptibility testing and counselling, as in the present study suggests, could lead to an unreasonable demand on GPs to interpret the results of genetic tests they have not ordered and are not trained to interpret. A large quantitative population study will be necessary to assess attitudes towards DTC genetic testing in a representative population and potential demand for genetic counselling.

3.5.3 Perceived impact of genetic susceptibility testing on stigma

Theories exist that a biological component for a mental illness shifts responsibility away from self to one's biology, thus reducing blame and consequently stigma associated with these disorders.[16, 34, 35] These findings are further supported by a study that found endorsement of genetic explanations decreased the likelihood of social acceptance of people with schizophrenia and major depressive disorder.[36]

Conversely empirical evidence suggests a genetic model for mental illness may increase the perceived seriousness of these disorders and increase stigma.[18, 34, 35]

The present study supports evidence that knowledge of genetic susceptibility will carry potential for both health promotion and harm through genetic validation versus genetic discrimination respectively. Further evaluation of public views about the effect of genetic susceptibility testing for psychiatric disorders on stigma is now required in a larger population. This is especially pertinent considering the current availability of DTC genetic susceptibility testing for allelic associations with various psychiatric disorders.

3.5.4   Limitations

Accuracy of the grouping of people with and without a personal or family history of mental illness cannot be guaranteed since data about participants' personal or family history of mental illness was collected through spontaneous self report. Voluntary reporting of a personal or family history of mental illness could be a limitation of the study since this may have resulted in the 'affected' group only represented by those willing to disclose such information. Intention to have a genetic test shown in this study may not be an true indication of uptake of a genetic susceptibility test for a multifactorial disorder since uptake has been shown to be lower than intention to test.[37] While the study aimed to set the questions to participants at reading level year 8, the study did not use measures to ensure all participants understood the genetic terms used. This may limit interpretation of data."

3.6   Conclusions

Hypothetical interest in future genetic susceptibility testing for depression risk alleles, especially among individuals with a personal or family history of mental illness, suggests there would be future demand for psychiatric genetic testing, potentially moderated by perceived discrimination and privacy issues. These

findings highlight the need for legislation to minimise the risk of potential genetic discrimination resulting from genetic susceptibility testing in psychiatry. Given the relatively low risk rates for close family members for developing psychiatric disorders with incomplete penetrance compared with Mendelian inherited traits, risks should be kept in perspective when informing the public and designing mental health interventions. These qualitative findings now require replication using a survey design in large representative non-clinical general population samples before recommendations about mental health interventions based on genetic risk can be made on a broader scale.

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4 STUDY 1B.

Community attitudes towards mental health interventions for healthy people on the basis of genetic susceptibility

4.1 Introduction

Rapid advances in genetic research over the past decade has led to identification of a substantial number of candidate genes associated with susceptibility to common complex disorders of public health significance including coronary artery disease, breast cancer, type 2 diabetes and major depressive disorder.[1]

Identification of groups with an increased genetic risk for such disorders presents an opportunity to target interventions that modify specific environmental risk factors at a pre-symptomatic stage, with the potential to significantly reduce burden of disease. Clinical utility, acceptability and potential health impact of pre-symptomatic genetic testing as a preventive intervention is currently the subject of contentious debate, but few data exist to guide policy and ethical decision-making.[2] Given current concerns about the rapid expansion of commercial genetic susceptibility tests for multifactorial diseases marketed DTC,[3] with many based on a small number of unreplicated studies with uncertain clinical validity, research about how the public might use genetic risk information to change health behaviour is needed.

Effective mental health intervention in psychiatry, based on genetic susceptibility, will depend upon community attitudes towards behavioural change to reduce risk, understanding of uncertain penetrance, the relationship between genes and environment, and potential to modify environmental risk factors.

Recent debate highlights popular attitudes about the right to know one's own genetic information,[4] and that genetic susceptibility tests, especially those available DTC, offer autonomy and empowerment for the individual.[5] Critics question whether it is responsible to offer genetic tests if their predictive value is low, and if there is no associated treatment available.[6] Implications cited include a potential for a low-risk result to provide false reassurance, or a high-risk result to cause fatalistic thinking based on a belief that a genetic component for a disorder makes the disorder less preventable.[7, 8] Both circumstances could demotivate an individual to engage in mental health interventions.[6]

Previous studies evaluating potential to change health behaviours in association with genetic risk information have focused on breast cancer,[9] heart disease,[7] nicotine depoendence,[10] familial hypercholesterolaemia,[7,11] and Alzheimer disease,[12] but not psychiatric disease. It is generally thought intention to change behaviour is a poor indicator of uptake of an intervention.[13] Fatalistic attitudes towards genetic risk for common complex disorders have been more commonly observed in general populations rather than among individuals informed of a genetic predisposition.[11] Empirical evidence suggests provision of genetic risk information to the individual may prompt uptake of new health behaviours.[9-11] Only anecdotal evidence is available about how genetic risk information involving psychiatric disorders might be interpreted and used by consumers.[14] As discussed in Chapter 3, the previously reported interaction between *5-HTTLPR,* exposure to stressful life events and increasing the likelihood of depression in non-clinical populations of adults,[15-18] adolescents[19] and children[20] was selected as a hypothetical example of a genetic susceptibility test. The conclusion of recent meta-analyses,[21, 22] published after the completion of the present study found no support for the association would not alter the approach taken in this study, although it would alter the specific genes to be tested.

4.2 Aims

Thus, using the example of serotonin transporter genotyping as a hypothetical genetic test, the present study aimed to qualitatively evaluate, among the general population, preparedness to modify risk for depression at a pre-symptomatic stage through preventive behaviour based on a hypothetical genetic susceptibility to depression.

4.3 Materials and Methods

The results reported here were undertaken as part of a broader qualitative study, which also explored interest in genetic testing for risk of major depressive disorder.[23] The results regarding the latter topic were reported in Chapter 3.

As this is a relatively unexplored area of enquiry, a qualitative methodology was used. See Chapter 3 for description of participants, focus group methodology, and methods for qualitative analysis. Codes were not used to link interest in genetic testing with responses in the present study.

4.4 Results

4.4.1 Participation and demographics

Participation and demographics were described in Chapter 3. See Table 1 for demographic characteristics of the sample.

4.4.2 Anticipated health behaviours if genetic test identified an increased risk of depression

The majority of participants (11 affected, 20 unaffected) thought being identified with an increased genetic risk for major depressive disorder would have a personal impact. Participants anticipated they would increase vigilance for symptoms, seek information about depression, make lifestyle changes, undertake preventive strategies or do nothing.

Increased vigilance

The majority of affected participants and about half of the unaffected participants agreed that receiving a genetic test result indicating an increased risk for depression would encourage them to be vigilant for signs and symptoms of the disorder. Several affected participants thought vigilance would make them more likely to act on warning signs for depression and seek medical help as appropriate:

> *"So if the symptoms and signs are showing up. .. you're aware so you're more likely to notice them."* [A].

One participant observed that public education about the familial aspect of depression would be an important intervention to enable family members to be vigilant for symptoms in each other [U]; while another remarked that this strategy could be life-saving [U].

Prompt information seeking

Many participants said an increased risk result would prompt them to seek information about depression, its symptoms and the meaning of being at increased genetic risk. One said:

> *"I'd want to get a better educated person … just understand what the implications may or may not be …."* [U].

Many participants showed trust in being advised by their doctors:

"But if I did have that sort of thing I would go and see the doctor and
do something because I wouldn't like to be caught out." [U].

One unaffected participant said she would "*go down the natural path*" rather than
see a GP [U]. Another pointed out that people with an increased genetic risk
should also be made aware of treatment options for depression and be advised on
how to access medical services [U].
 One participant, despite suggesting he would seek further information if he
received an increased risk result, revealed a fatalistic view that could negatively
impact on effectiveness of genetic counselling and behavioural intervention:

"It's a done deal isn't it? You've got your DNA, you've got your
genetics and you're in no position to alter them," [U].

Prompt lifestyle changes

Participants who said they would make lifestyle changes if genotyping identified
an increased risk for depression considered the potential to modify environmental
risk factors including stress, diet, exercise and drug and alcohol intake. Several
participants were in favour of minimising stress as an intervention:

"You'd have to try and get as many stresses out of your life as
possible…if you've got a stressful job, get rid of the job," [U].

Other participants, while agreeing that drugs and alcohol intake were modifiable
risk factors, were cautious about whether stress could be modified or avoided:

"…you can cut down … the drugs and alcohol and stress you can try
but you're not going to erase that from your lifestyle," [U].

"Yeah, .. marijuana and drugs and alcohol..definitely something to
be avoided if you've got a disposition but you can't avoid stress
throughout life, you just can't," [A].

One participant said a genetic test result indicating an increased risk for depression would encourage him to maintain a healthy lifestyle [U]; while another remarked she would adjust her diet and take more exercise as well as *"seek some sort of help so as you can be steered in the right direction,"* [A]. Two participants observed that individual differences in response to stress would impact on attempts to implement preventive strategies [A] [U].

Prompt preventive behaviour

One participant, who disclosed a history of depression, commented that genetic susceptibility testing, had it been available to her prior to her diagnosis, would have enabled her to learn coping strategies in advance so that her depression *"could possibly have been minimalised or prevented,"* [A]:

> *"I would have liked to have known [in advance] because the things I've learnt how to cope with it over time like panic attacks...how to breathe properly...I think maybe I could have implemented some of those tools earlier. It might have stopped me from getting really sick when I did,"* [A].

Another participant said if she received an increased risk result she would start a course of anti-depressants as a preventive strategy [A]. Two participants agreed preventive medication could be used as a preventive measure while observing there could be potential for harm [U] [U]; while two were against such a strategy [A] [A].

Do nothing

Two of the four unaffected participants who said they would do nothing if they received a genetic test result that showed an increased risk for depression expressed the views: *"...why treat something if you don't have it?"* [U] and *"...why educate yourself on something and worry yourself when it's probably not going to happen."* [U].

4.4.3   Causal attributions for mental illness

The study found support for a genetic model for major depressive disorder with genetic factors viewed as predisposing rather than causal. Some participants perceived depression as less severe, less enduring and more likely to be attributed to stress rather than genetic factors than other psychiatric disorders including bipolar disorder and schizophrenia. Two participants observed that individual differences in response to stress would impact on attempts at preventive strategies.

Both affected and unaffected participants suggested that possible environmental factors that could trigger a mental illness were "*alcohol, drugs, stress, chemical imbalance, poverty, general trauma, emotional disturbance, relationship breakdown, family environment, isolation, trauma in childhood, social environment, disadvantage*" and "*arguments all the time.*"

4.5   Discussion

The present study supports previous findings that positive attitudes towards a range of mental health intervention strategies at a pre-symptomatic stage exist.[24] These include interest in obtaining information and genetic counselling from GPs about the implications of having a genetic test result indicating an increased risk for major depressive disorder, information about depression, its risk factors and symptoms, and about future options for treatment and management. There was minor support for preventive medication among affected individuals as a pre-symptomatic intervention.

Although some participants were ambivalent about whether stress could be modified, positive attitudes were reported towards willingness to engage in lifestyle interventions such as reducing stress, drugs and alcohol intake and increasing exercise. The results suggest mental health interventions that facilitate learning of effective coping skills are likely to be well-received as preventive strategies for target groups at a pre-symptomatic stage. Genetic risk information

that prompts prescribed preventive behaviours may also motivate individuals to pursue unproven therapies or treatments that may be inappropriate or harmful.[25]

A number of findings have the potential to moderate uptake of future molecular-based preventive mental health strategies among individuals identified as an increased risk for depression. These include fatalistic attitudes that one's DNA is immutable thus rendering environmental modification useless, perceptions of pointlessness of interventions in the absence of symptoms, and mixed or confused views on casual attributions for major depressive disorder.

Finding community endorsement of a contribution of both genetic and environmental factors in the development of mental illness and perceptions that genetic predispositions can be modified by adjusting environmental risk factors supports previous studies.[26-28] These endorsements suggest target groups might be receptive to preventive programs that involve genetic susceptibility testing associated with preventive cognitive and behavioural interventions that modify environmental risk factors. This is especially true in the light of greater endorsement of environmental risk factors as a cause for major depressive disorder than other psychiatric disorders.

As provision of information about individual genetic risk alone may not be sufficient to change health-related behaviour[4, 5, 29] it will be necessary to evaluate the synergistic effects of individual genotype with personal and family history of psychiatric disorders, and lifestyle and environmental factors that regulate gene expression.[14, 16]

Ethical issues surrounding the use of genetic susceptibility testing in psychiatry, such as risk of discrimination and loss of privacy, require further investigation. Effective mental health interventions and appropriate genetic counselling should be established before depression risk genotyping is offered in clinical practice.

4.5.1 Limitations

Some participants may have interpreted the term 'significant adversity', or stressful life events, to mean everyday life stress, which could have affected anticipated health behaviour based on perception of modifiable nature of risk factors. Intention to change health behaviours in response to genetic risk information shown in this study may not reflect actual change. While every effort was made to include all participants throughout the focus group discussion, there may be a bias towards the views of a dominant minority. Reporting of a personal or family history of mental illness was voluntary, which may have resulted in the affected group only represented by those willing to disclose such information. While the study aimed to set the questions to participants at reading level year 8, the study did not use measures to ensure all participants understood the genetic terms used. This may limit interpretation of data.

4.6 Conclusions

This qualitative study has only identified the range of attitudes towards anticipated health behaviours based on genetic risk information, and not the extent to which they are held. These qualitative findings now require quantitative replication using a survey design in large representative non-clinical general population samples before recommendations about mental health interventions based on genetic risk can be made on a broader scale.

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5 STUDY 2A.

Community interest in genetic testing for susceptibility to major depressive disorder in a large national sample.

5.1 Introduction

Identifying healthy individuals with genotypes that suggest increased risk of psychiatric illness provides an opportunity to reduce the burden of disease through environment-specific intervention at a pre-symptomatic stage. Disclosure of genotyping information about risk for Alzheimer disease[1] or major depressive disorder[2] to asymptomatic adults has been shown to provide a benefit to individuals with 'low risk' variants and to cause low to modest distress to those with an 'increased risk' variant. Although most genetic testing is currently available only through a health care provider, an increasing range of tests are being offered DTC[3] without medical supervision, raising concerns about the psychosocial impact of risk disclosure. This has stimulated popular debate about the right to know or not to know one's own genetic information, and whether genetic susceptibility tests, especially those available DTC, provide useful information about one's health.[4] Many genetic tests offered DTC involve unreplicated gene-disease associations and have uncertain predictive value and clinical utility.[5] Furthermore, without medical supervision, consumers may be at risk of making uninformed health decisions.[6]

Few data exist on both the determinants of community interest in such testing and its psychosocial impacts. Given current international concern about unregulated genetic susceptibility testing, such data are urgently required to inform national and international policy development.

Previous studies on attitudes towards genetic testing for susceptibility alleles thought to be involved in some mental illnesses have been predominantly limited to preliminary and/or qualitative studies involving people with an unspecified psychiatric diagnosis,[7] people with multiple relatives affected by bipolar disorder [8-12] or schizophrenia [13, 14] and psychiatrists.[10, 11, 13] These studies have generally found positive attitudes towards genetic susceptibility testing for predisposition to psychiatric disorders. One recent quantitative study involving families with a high density of bipolar disorder showed that interest in hypothetical genetic testing increased with the degree of certainty indicated by the test.[9] Further recent studies reported strong support for genetic testing for predisposition to psychiatric disorders but were limited to people with a diagnosis of major depressive disorder, bipolar disorder, schizophrenia and/or anxiety disorders participating in psychiatric genetic studies.[15, 16] The qualitative study 1A reported in Chapter 3 found positive public interest in depression risk genotyping, which was influenced by the potential for discrimination and loss of privacy.[17] Participants showed trust in obtaining such a test through the medical system but were wary of DTC genetic testing services.

The present investigation is the first national population study to examine this issue for genetic variations associated with mental health in general. This study uses the hypothetical example of serotonin transporter genotyping as it has been previously reported to convey a gene-environment risk for major depressive disorder,[18-23] as discussed in Chapter 2.2.

The present study proposes the following hypotheses: interest in genetic testing for a depression-risk genotype will be (i) greater if available from a doctor rather than DTC via the internet; and be positively associated with (ii) having a personal history of mental illness; and (iii) lower perceived social stigma attached to mental illness.

5.2 Methods

Participants across Australia were recruited by a contracted market research company in May 2008 using random digit dialling of a computer-generated list of landline phone numbers that uses prefixes based on the geographic coverage of the sample's area, with the aim of producing a nationally representative sample. Respondents were selected from each household using a Computer Assisted Telephone Interviewing (CATI)-generated algorithm. Only those aged 18 years or more, and fluent in English were eligible to participate. Only one individual per household could participate. A target sample size of at least 1000 completed CATI interviews was reached. Ethical approval for the study was provided by the relevant Institutional Review Board.

5.2.1 Measures

Demographic characteristics
Data on sex, age, highest level of education achieved and current marital status were collected using specifically designed multiple-choice items.

Clinical and family history data
Data on self-estimation of risk of depression were collected in a three-part question early in the survey: 'Compared with the average person, would you say your risk of depression is higher than average; lower than average; the same as the average person?'

Self-reported data on personal history of mental illness and exposure to mental illness through close relatives or close friends were collected on completion of the survey. Participants were asked 'have you' or 'has a close relative or friend ever been diagnosed with depression, bipolar disorder or schizophrenia?' These terms were defined to participants.

Causal attributions for mental illness

Causal attributions to assess the perceived importance of different factors in causing a mental illness were derived from Meiser et al.[24] Participants responded to all items using a five-point Likert-type scale ranging from 1 'Not at all important' to 5 'Extremely important'. For statistical analysis, items were grouped according to the exploratory factor analysis of Meiser et al which yielded a four factor solution with item groupings representing (i) genetics, (ii) life stress, (iii) abuse and (iv) family environment.[24]

Three items with five-point Likert-type response options were used to assess degree of endorsement of perceptions about: gene-environment interactions as a causal mechanism (framed as 'mental illnesses are caused by an interplay of genetic risk and stressful life experiences'), incomplete penetrance as a mechanism of inheritance (framed as 'it is possible to have a genetic risk for a mental illness but never actually get the disorder'), and no causal genetic factors (framed as 'it is possible to have a mental illness without a genetic risk').

Stigma

Perceptions about the impact of evidence for a genetic component for mental illness on stigma were explored using a three-point scale ranging from 'stigma would decrease', 'a genetic basis for a mental illness would make no difference to stigma' and 'stigma would increase'.

Perceived benefits and disadvantages

Perceived benefits and disadvantages of genetic susceptibility testing were assessed using 12 items (see Figure 1 for item wording) with five-point Likert-type response options ranging from 1 ('Strongly disagree') to 5 ('Strongly agree'). The measure is based on the results of Study 1A reported in Chapter 3,[17] and assesses respondents' perceptions of what 'most other people' believe. These measures demonstrated good internal consistency in the present samples, with Cronbach's α = 0.65 (benefits) and α = 0.76 (disadvantages). Summary scores were calculated for perceived benefits and disadvantages separately, with higher values indicating greater endorsement of perceived benefits or disadvantages.

5.2.2   Outcome variable

Interest in having genetic testing for depression risk

Data on interest in genetic susceptibility testing was collected by i) channel of access (i.e via a doctor or DTC) and ii) before and after participants were asked about perceived benefits and disadvantages of genetic susceptibility testing. The latter two will be reported below as 'naïve interest' and 'considered interest', respectively. This produced four variables: naïve interest in having the test through a doctor; naïve interest in having the test DTC; considered interest in having the test through a doctor and considered interest in having the test DTC. Interest in having depression risk testing was assessed by one item with four Likert-type response options ranging from 'no, definitely not', 'no, probably not', 'yes, probably', to 'yes, definitely' plus 'don't know'.

Questions were framed as: 'If a genetic test to determine your risk for developing depression in the event of experiencing stressful life events was available through 1) your own doctor, 2) via the internet directly to you from an overseas laboratory, would you be interested in having it?'

Since the public health system is likely to be a future provider of genetic susceptibility testing to informed patients, 'considered interest in genetic testing through a doctor' was selected as the most appropriate outcome variable for the purposes of multivariate analyses. This variable was re-coded into a binary variable by merging 'definitely' and 'probably' options and redefining the new variable as 'yes, would consider' versus 'no, would not consider' genetic testing. 'Don't know' responses were not included in the new variable.

5.2.3   Statistical analyses

Data were explored initially with descriptive statistics. Chi-square cross tabulations were analysed for naïve and considered interest through a doctor and

through DTC channels. Bivariate associations between possible predictor variables and the outcome variable were first examined using independent samples t test for continuous predictor variables, Mann–Whitney U tests for ordinal predictor variables and Pearson's chi-square cross tabulations for categorical predictors. All variables with a bivariate association with $p<0.1$ were entered into a backward stepwise removal regression model until the only remaining variables were those with $p<0.05$.

The following variables were assessed as possible predictor variables in the analysis of considered interest in depression-risk testing through accredited medical services: personal history of a mental illness, experience of a mental illness through a close relative or close friend, self-estimation of risk for major depressive disorder, causal attributions for mental illness, gene-environment interaction as a causal mechanism, incomplete penetrance as a hereditary mechanism, no causal genetic factors, perceived impact of a genetic component for mental illness on social stigma, and perceived benefits and disadvantages of having such a genetic test. All regression analyses were adjusted for age, sex and education level.

5.3   Results

5.3.1   Participant characteristics

Of the 1544 eligible individuals contacted, 498 declined, resulting in 1046 completed surveys and a participation rate of 68%. Sociodemographic characteristics of the 637 (61%) female and 409 (39%) male participants, with a mean age of 50.7 years (range 18-88) years, are presented in Table 3.

Table 3. Summary of participant characteristics (Maximum N=1046)

Variable	*N*	*(%)*
Sex		
Male	409	(39.1)
Female	637	(60.9)
Age (mean (S.D) = 50.7 years (16.2), range 18-88)		
18-29	111	(10.6)
30-39	169	(16.2)
40-49	221	(21.1)
50-59	212	(20.3)
60+	330	(31.6)
Current marital status		
Married/*de facto*	661	(63.2)
Other	384	(36.8)
Country of birth		
Australia	815	(78.0)
Outside Australia	230	(22.0)
Highest level of education		
No post school education	473	(45.4)
Post-school education	569	(54.6)
History of mental illness		
Personal[a]		
Yes	237	(22.7)
No	805	(77.3)
Close relative/friend[b]		
Yes	661	(63.7)
No	337	(36.3)
Self estimation of risk for major depressive disorder[c]		
Higher than average	240	(23.2)
Lower than average	295	(28.5)
Same as average	500	(48.3)

Values are given as *n* (%). [a]Refers to personal history of depression, bipolar disorder or schizophrenia. [b]Refers to experience of depression, bipolar or schizophrenia through a close relative or close friend. [c]Refers to personal estimation of risk for major depressive disorder compared to average population risk.

5.3.2 Perceived benefits and disadvantages of genetic testing for depression risk

Figure 1 details the proportions of participants who agreed or strongly agreed with a range of perceived benefits and disadvantages of genetic testing.

5.3.3 Interest in genetic testing for depression risk by channel of access

Interest in depression-risk genotyping varied according to channel of access (doctor versus DTC via the internet) and before versus after consideration of positive and negative implications, information about which was provided during the telephone interview ('naïve interest' versus 'considered interest'). When naive, 60% of participants were interested in depression-risk genotyping through a doctor, which marginally increased to 63% after consideration. When naïve, 49% of participants were interested in accessing the same test DTC through the internet, which significantly decreased to 40% once given the opportunity for consideration (N=981, χ^2=476, df=1, p<0.001). Interest in accessing depression-risk genotyping through a doctor was significantly greater than interest accessing such a test DTC in both cases, when either naïve (p<0.001) or considered (p<0.001).

Figure 1. Percentages of participants indicating agreement or strong agreement with a range of perceived benefits and disadvantages of depression risk genotyping. (Maximum N = 1046).

BENEFITS

If the genetic test showed you were at lower than average risk

You would get peace of mind — 81.0

You would see yourself as being resilient to depression regardless of any stresses in your life — 57.5

If the genetic test showed you were at higher than average

You would be ready to get early psychological help — 85.7

You would be able to start to minimise stress factors in your life — 83.2

It could tell you what treatment might be most effective for you — 82.2

It could help legitimise depression as a biological disorder — 81.7

DISADVANTAGES

If the genetic test showed you were at higher than average

You would be afraid of being discriminated against by insurance companies or employers — 64.0

You would start worrying about depression that may never develop — 62.4

You may be more likely to feel depressed — 58.7

You would worry the result may not stay private — 53.7

You would be afraid of being labelled or stigmatised — 52.4

It could trigger a mental illness just by knowing you might have an increased risk — 46.4

Percentage: 0 20 40 60 80 100

5.3.4 Factors associated with considered interest in genetic testing for depression risk.

Tables 4a and 4b show results from bivariate analyses of factors associated with considered interest in depression-risk genotyping. Considered interest in depression-risk genotyping was significantly and positively associated with having a personal history of a mental illness; self-estimation of having a higher than average risk for major depressive disorder; being female; having no post-school education; endorsement of perceived benefits of having such a test; perceiving genetics, life stress and/or abuse as causal attributions for mental illness; and perceiving gene-environment interaction as a causal mechanism. Among participants who thought evidence of a genetic component would affect stigma associated with mental illness, a significantly greater proportion believed stigma would increase rather than decrease (N=670, 72% vs 28%, p<0.001). Despite this, we found considered interest in having depression-risk genotyping was significantly associated with beliefs that social stigma would increase.

Table 4a. Items assessed for association with considered interest[i] in depression risk genotyping (Maximum N=1046).

Variable	Interest in testing[i] N	%	χ^2	p
Sex				
Male	234	58.1		
Female	410	65.5	5.78	0.016[h]
Highest level of education				
No post school education	309	66.6		
Post school education	333	59.4	5.68	0.017[h]
History of mental illness				
Personal[a]				
Yes	189	81.8		
No	455	57.3	46.4	<0.001[h]
Close relative/friend[b]				
Yes	402	62.0		
No	239	64.1	0.42	0.52
Self estimation of risk for major depressive disorder[c]				
Higher than average	182	77.1		
Same as average	324	66.1		
Lower than average	132	45.2	61.63	<0.001[h]
Beliefs about social stigma[d]				
Genetic component increases stigma	338	70.9		
No effect on stigma	153	54.6		
Genetic component decreases stigma	98	52.7	29.22	<0.001[h]

[a]Refers to personal history of a mental illness (depression, bipolar disorder or schizophrenia), [b]Refers to experience of depression, bipolar or schizophrenia through a close relative or close friend. [c]Refers to personal estimation of risk for majo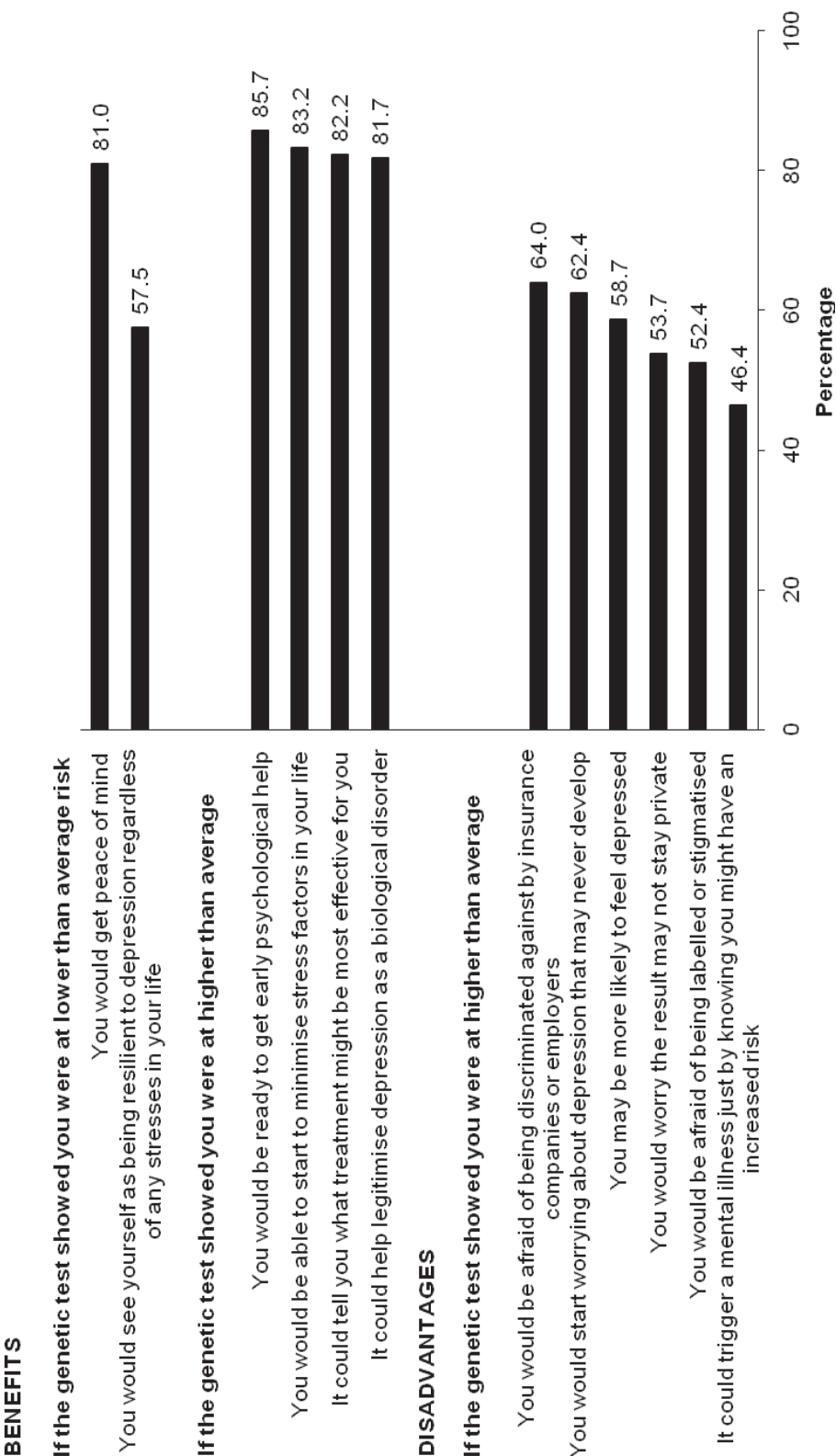r depressive disorder compared to average population risk. [d]Beliefs about social stigma refers to belief that genetic evidence for mental illness would increase or decrease stigma. χ^2 values are from Pearson's chi square tests. [h]p values <0.1 entered into logistic regression.

[i]Refers to considered interest in genetic testing through a medical clinic.

Table 4b. Items assessed for association with considered interest[i] in depression risk genotyping (Maximum N=1046).

Variable	Interested in testing[i]			Not interested in testing[i]			z/t	p
	N	Mean	(S.D)	N	Mean	(S.D)		
Endorsement of benefits or disadvantages of testing[e]								
Endorse benefits	644	4.1	(0.5)	385	3.8	(0.7)	8.35	<0.001[h]
Endorse disadvantages	644	3.4	(0.8)	385	3.5	(0.8)	1.83	0.068[h]
Endorsement of causal attributions[f]								
Genetics	644	4.5	(0.9)	385	4.5	(1.0)	2.15	0.032[h]
Abuse	644	4.6	(0.6)	385	4.4	(0.8)	5.16	<0.001[h]
Life stress	644	3.7	(0.8)	385	3.9	(1.0)	5.15	<0.001[h]
Family environment	644	4.1	(0.9)	385	3.8	(1.0)	4.86	<0.001[h]
Gene-environment interaction	618	4.1	(0.7)	368	3.9	(0.8)	2.23	0.026[h]
Incomplete penetrance	597	4.0	(0.8)	359	3.9	(0.8)	1.18	0.238
No genetic factors	604	4.1	(0.8)	368	4.1	(0.7)	0.77	0.439
Age	643	50.5	(16.7)	384	50.9	(15.5)	0.39[g]	0.694

[e]Endorsement of benefits, disadvantages of depression risk genotyping, and [f]causal attributions of mental illness: range 1 to 5, with higher values indicating greater endorsement. values are absolute values from Mann Whitney-U tests. [g]t value is from independent samples t test. [h]p values <0.1 entered into logistic regression. [i]Refers to considered interest in genetic testing through a medical clinic.

When these variables were entered into a logistic regression model using a backward stepwise (likelihood ratio) elimination method, personal history of mental illness (OR=2.58, p<0.001), higher than average self-estimation of risk for major depressive disorder (OR=1.91, p<0.001), endorsement of benefits of testing for a depression-risk variant (OR=3.47, p<0.001), the belief that genetic evidence for mental illness would increase social stigma (OR=1.60, p<0.001), were all significantly and positively associated with considered interest in depression-risk genotyping after controlling for sex and education level. Significant negative predictors of interest were perceived disadvantages of depression risk genotyping (OR=0.80, p=0.018) and age (OR=0.99, p=0.047) (Table 5).

Table 5. Final model of logistic regression analysis predicting factors influencing interest[i] in having depression risk genotyping after controlling for demographic factors. N=930.

Variable	B	OR	OR 95% CI	p
Personal history of mental illness	0.95	2.58	1.66 to 4.00	<0.001
Self-estimation of risk for depression higher than average	0.65	1.91	1.91 to 1.52	<0.001
Endorsement of perceived benefits of depression risk genotyping	1.24	3.47	2.58 to 4.66	<0.001
Endorsement of perceived disadvantages of depression risk genotyping	-0.23	0.80	0.66 to 0.96	0.018
Belief genetic evidence for mental illness will increase social stigma	0.47	1.60	1.32 to 1.94	<0.001
Age	-0.01	0.99	0.98 to 1.00	0.047
Sex	0.19	1.21	0.90 to 1.64	0.214
Education level	-0.17	0.85	0.70 to 1.03	0.093

Final model: -2 log likelihood ratio = 1030.686, Cox and Snell R square = 0.191, Nagell Kerke R square = 0.260. p<0.001. [i] Refers to considered interest in genetic testing through a medical clinic.

5.4 Discussion

This large, national population-based study suggests that formal medical services are likely to be the preferred channel for accessing genetic susceptibility testing as demonstrated in this example of serotonin transporter genotyping for depression-risk. This preference was significantly higher compared to interest in accessing genetic tests DTC after considering benefits and disadvantages of genetic susceptibility testing. Nevertheless, considered interest in accessing such a test commercially prevailed, suggesting that concerns about the availability of unregulated DTC genetic testing need to be addressed. This finding supports results of the qualitative study 1A (Chapter 3), which demonstrated greater trust amongst participants in obtaining such a test through the medical system, with interest modified by concerns about genetic discrimination and loss of privacy.[17]

Sixty-three percent of the 1029 participants who answered the question indicated considered interest in having genetic susceptibility testing for susceptibility to depression, if it were available. This level of interest is similar or marginally lower than that reported in previous studies that have demonstrated rates of interest in genetic susceptibility testing of 61%,[1] 69%,[10] 83%[13, 15] and 97%[11] for susceptibility to Alzheimer disease, bipolar disorder,[9-12] schizophrenia,[13, 14] psychiatric disorders in general[7, 15, 16] in relatively small groups with direct experience of the illness including patients, relatives and professionals. The lower rate of interest demonstrated in this large national sample is likely to reflect a more realistic indication of community interest in genetic testing for depression risk and other psychiatric conditions. Actual uptake of such testing once clinically available could be lower than predicted by intention to test.[25]

The present study identified strong positive significant associations between considered interest in genetic testing for susceptibility to depression and personal self-reported history of mental illness; a higher than average self-estimation of increased risk for major depressive disorder; endorsement of the perceived benefits of having such a test; and a belief that a genetic explanation for mental illness

would increase social stigma linked with the disorder. These associations were independent of sex and level of education. Endorsement of perceived disadvantages of depression risk genotyping and age were significant negative predictors of interest.

The finding that perceived personal susceptibility to the disorder is a strong predictor of interest in genetic susceptibility testing is consistent with that reported for other multifactorial disorders such as heart disease,[26] schizophrenia,[13] bipolar disorder,[9, 10, 12] and psychiatric disorders in general.[7] However, predictors of uptake of genetic susceptibility testing in clinical situations may differ. Uptake rates are likely to be influenced by differences in patient perceptions about predictive validity of the genetic test in question; potential benefits of such a genetic test, such as accessing early help; potential disadvantages such as employment and insurance discrimination; and differences in implications for members of affected families.

The finding of a significant positive association between considered interest in genetic testing for susceptibility to depression and endorsement of perceived benefits of having such a test; and a significant negative association with endorsement of perceived disadvantages, supports prevailing beliefs that perceived benefits may outweigh risks.[12] The most frequently rated perceived benefits – a greater preparedness for accessing early psychological help and minimising stress – are consistent with beliefs reported in a previous study that such testing could facilitate prevention and earlier intervention of major depressive disorder.[2] The findings also confirmed perceptions that potential for discrimination by insurance companies or employers was the most frequently identified disadvantage of genetic testing for susceptibility to depression. Several governments have issued a ban on marketing genetic tests for common complex disorders directly to the consumer in the absence of appropriate regulation.[3, 27, 28] Despite the signing of the Genetic Information Nondiscrimination Act into law in 2008 in the United States, where many of the commercial vendors of DTC genetic tests are based, there may be no guarantees of protection against discrimination.[29] Considering DTC genetic tests are marketed internationally, consumers may have no legal protection from

genetic discrimination for insurance or employment in their own country. The recent proposal to introduce a mandatory registry of genetic tests aims overcome some of these problems and improve the genetic testing system by providing the public and health providers with accurate, reliable, and validated information about the options available before decisions are made about obtaining a genetic test.[30] Thus, the study's findings highlight that while genetic susceptibility testing as an intervention tool for target groups is likely to be acceptable to the general community, they indicate the need for appropriate legislation to prevent genetic discrimination if such interventions are to be effective.

Finding a significant positive association between beliefs that evidence of a genetic component for mental illness would increase rather than decrease social stigma and considered interest in having genetic testing for susceptibility to depression at first appears contradictory. However, this finding suggests that any social stigma connected to beliefs about the roles of genes in mental illness is unlikely to discourage individuals from having such a test. It could be that perceived personal benefits of having genetic testing for susceptibility to depression outweigh concerns about social stigma, that major depressive disorder is perceived as less likely to have a genetic basis than other mental illnesses, or that there is less stigma attached to depression than bipolar disorder and schizophrenia. The significant negative association between interest in testing and age may indicate that individuals over a certain age perceive genetic susceptibility testing for an adolescent/adult onset disorder such as major depressive disorder as having little relevance.

5.4.1   Limitations

It should be noted that the use of landline telephone numbers may have skewed the sample towards older age groups and females, consistent with reported participation bias in public health surveys.[31, 32] The present study used strategies known to minimise self-selection bias caused by non-response, including randomisation of participant selection per household, achieving a moderately high

participation rate, and controlling the results for demographic confounders statistically.[33]

It is possible that by asking participants to consider their responses in terms of depression, bipolar disorder, and schizophrenia initially could have confounded the later answers that focused specifically on depression. However, including bipolar disorder and schizophrenia in addition to depression in questions about stigma (chapter 5) and causal attributions (chapter 6) provides a good basis upon which to evaluate public attitudes towards psychiatric genetics in general.

It is possible that the inclusion of 'close friends' as well as close relatives in the variable to determine the effect of life exposure to mental illness on interest in testing may account for the finding that family history was not significantly associated with interest in genetic testing for major depressive disorder. It would be beneficial to separate these variables in future.

Other limitations relate to the possibility that some participants may have interpreted the term 'life stress' to mean everyday life stress rather than significant stressors associated with mental illness, such as child abuse, which could have affected interest in testing based on perceptions about the modifiable nature of risk factors. Attitudes towards genetic testing for susceptibility to a psychiatric disorder may be influenced by naivety about low predictive power of such tests. The low risk rates for first-degree relatives for developing psychiatric disorders with incomplete penetrance compared with Mendelian traits should be kept in perspective when informing the public and designing mental health interventions. Survey methods as employed by this research have limited power to predict future human behaviour. This should be considered when interpreting the findings. While the study aimed to set the questions to participants at reading level year 8, the study did not use measures to ensure all participants understood the genetic terms used. This may limit interpretation of data

5.5   Conclusions

This is the first study to provide data from a large national cohort in which the determinants of community interest in genetic susceptibility testing for mental illness and its psychosocial impacts have been investigated. Using the example of testing for a genetic variant for depression risk. The results indicate that, there is likely to be strong interest in genetic susceptibility testing for a complex trait such as major depressive disorder if it were to become available, even though the predictive validity and clinical utility of such tests remains unclear. It is likely that interest will persist despite finding attitudes that genetic links to mental illness would increase rather than decrease stigma. The study provides objective data in place of the current subjective commentaries on community concern about unregulated genetic susceptibility testing. Large population surveys such as that reported here will be important in informing public debate, public education programs and policymaking.

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6 STUDY 2B.

Community attitudes to genetic susceptibility-based mental health interventions for healthy people in a large national sample

6.1 Introduction

Despite an apparent high interest in genetic testing for susceptibility to common multifactorial disorders among individuals with an affected relative[1-7] and among the general population unselected for disease risk,[8-11,12] few data describe anticipated health behaviours as a consequence of such testing.

The present investigation is the first national population study to examine this issue for genetic variations associated with mental health in general. This study uses the hypothetical example of serotonin transporter genotyping as it has been previously reported to convey a gene-environment risk for major depressive disorder.[13-18] Currently, serotonin transporter genotyping is not commercially available as a genetic test to predict risk for major depressive disorder, but has been marketed for the purposes of predicting individual response to selective serotonin reuptake inhibitor antidepressants.[19]

Previous studies have primarily focused on health behaviours following predictive genetic testing for Mendelian disorders such as hereditary breast, ovarian, and colorectal cancer.[20, 21] Comparisons are limited because gene mutations for these disorders are highly penetrant and there are specific guidelines for screening, surveillance, and surgery are well-known.

Although many predictive genetic tests are only currently available through a health care provider with linked genetic counselling, an increasing range of genetic susceptibility tests for multifactorial disorders are now marketed DTC via Internet

sites, many of which bypass health care providers and appropriate counselling.[9] Recent population-based surveys also show relatively high interest in DTC genetic tests for susceptibility to breast cancer,[1] major depressive disorder[12] and tests relating to lifestyle (nutrigenomics).[22]

The provision of genetic susceptibility tests to healthy people for common multifactorial disorders is controversial because some gene-disease associations are yet to be replicated, the predictive validity of such tests may be low, and clinical utility is yet to be determined. Successful preventive mental health interventions based on an integration of genetic and environmental risk will depend on public understanding of and responses towards personal genetic risk information.

The extent to which genetic risk information promotes changes in health-related behaviours involving gene-disease associations with uncertain penetrance, such as heart disease,[23] familial hypercholesterolaemia,[23,24] nicotine dependence,[25] Alzheimer disease[26] and major depressive disorder[27] remains unclear. It has been argued that genetic susceptibility test results indicating low risk for a disorder should provide relief and reassurance, while test results indicating increased risk are expected to prompt health protective behaviours.[28] Rather than facilitating protective behavioural change some evidence suggests that genetic risk information could induce fatalistic attitudes about modifiability of disorders with associated genetic susceptibility, thus inhibiting willingness to engage in protective health behaviours.[23, 24, 29, 30]

This study aims to assess preparedness to modify risk for major depressive disorder at a pre-symptomatic stage through preventive behaviour based on a hypothetical genetic susceptibility. Because few studies have evaluated behavioural response to genetic susceptibility testing, Leventhal's Common Sense Model of Self-regulation[31] is used to provide a theoretical framework. This model posits that health behaviours in response to risk for disease depend on how preventable, controllable or curable the disease is perceived to be.

The qualitative study 1B,[27] reported in Chapter 4, found a likely public demand for preventive mental health interventions for healthy people on the basis of genetic susceptibility if genetic susceptibility testing were to become available in psychiatry. Based on the results of this study[27] and using the theoretical framework of Self-Regulation Theory, [31] the present study tested the following hypotheses: Willingness to engage in health behaviours that could ameliorate risk for major depressive disorder based on a hypothetical genetic susceptibility will be positively associated with i) a personal history of a mental illness, ii) self-perception of being at increased risk for major depressive disorder, and iii) endorsement of gene-environment interaction as a causal mechanism for mental illness.

6.2   Methods

Methods regarding recruitment, CATI-generated algorithm, eligibility and target sample are described in Chapter 5.

6.2.1   Measures

Methods for evaluating predictor variables including demographic characteristics, self-estimation of risk for major depressive disorder, personal and family history of mental illness, and causal attributions for mental illness are described in Chapter 5.

6.2.2   Outcome variables

Anticipated health behaviours in the event of receiving a major depressive disorder risk genetic test result

Based on the results of the qualitative study 1B reported in Chapter 4,[32] a range of perceived health behaviours were explored using five-point Likert-type response options ranging from 'Strongly disagree' to 'Strongly agree'. Participants were told, "If you were found, through genetic testing, to have an increased risk for major depressive disorder in the event of stress, how much do you agree or

disagree with the following possible changes you might make to your lifestyle?" Five potential health behaviours triggered by being hypothetically identified as having increased risk for major depressive disorder were: 'You would start therapies or courses that would help you learn to develop better strategies to cope with stress';' You would modify potential stressors in your life such as stressful job, relationship or domestic situation'; 'You would reduce excessive drug or alcohol use;' You would help your children learn how to be more resilient to stress in case they were also at increased risk for major depressive disorder'; and, 'You would decide to not to have children.'

6.2.3   Statistical analyses

Data were explored initially with descriptive statistics. Bivariate associations between possible predictor variables and outcome variables were first examined using Spearman's rank correlations (r_s) and Mann–Whitney U tests for ordinal predictor variables and Pearson's chi-square cross tabulations for categorical predictors. All variables with a bivariate association with $p<0.1$ were entered into a backward stepwise removal regression model until the only remaining variables were those with $p<0.05$.

The following variables were assessed as possible predictor variables in the analyses of anticipated health behaviours in response to receiving genetic test result that suggests a higher than average hypothetical risk for major depressive disorder: personal history of a mental illness, experience of a mental illness though a close relative or close friend, self-estimation of risk for major depressive disorder, causal attributions for mental illness, gene-environment interaction as a causal mechanism, incomplete penetrance as a hereditary mechanism and no causal genetic factors. All regression analyses were adjusted for age, sex and educational level.

6.3 Results

Of the 1544 eligible individuals contacted, 498 declined, resulting in 1046
completed surveys and a participation rate of 68%. Sociodemographic
characteristics of the 637 (61%) female and 409 (39%) male participants, with a
mean age of 50.7 years (range 18-88) years, are presented in Chapter 5, Table 5.

Figure 2 shows the frequency of endorsement of perceived importance of different
factors in causing mental illness.

Figure 3 details the proportions of participants who agreed or strongly agreed with
a range of anticipated health behaviours in response to receiving a major
depressive disorder risk genetic test result.

Results from bivariate analyses of factors associated with anticipated health
behaviours in the event of receiving a major depressive disorder risk genetic test
result are shown in Tables 6 and 7.

Figure 2. Frequency of endorsement of risk factors perceived as important or very important to the development of mental illness (N=1046).

Perceived risk factors

Genetics
- 'Imbalance of brain chemicals' — 86.3
- Genetics — 69.2

Abuse
- Sexual abuse — 86.5
- A difficult or abusive childhood — 82.8

Life stress
- Accumulation of daily life stresses — 66.8
- Major life changes — 64.5

Family environment
- Family environment — 68.8
- Parental behaviour — 66.6
- Difficult marriage/relationship — 65.7
- Personality factors — 46.0

Perceived causal mechanisms

- Incomplete penetrance — 83.7
- Gene-environment interaction — 80.3
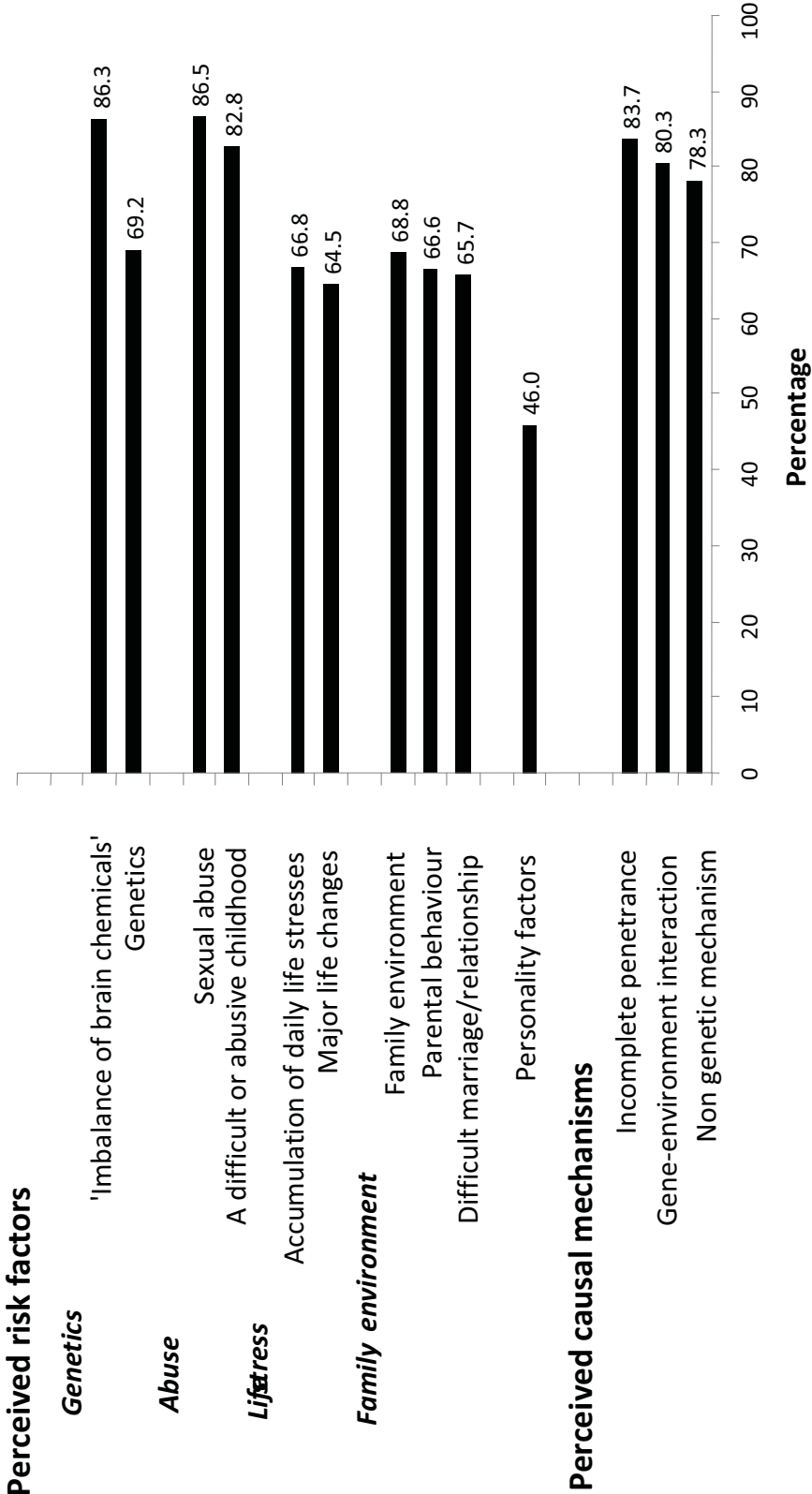- Non genetic mechanism — 78.3

Percentage

Figure 3. Anticipated health behaviours in response to receiving a hypothetical genetic test result indicating higher than average risk for depression (N=1046).

Table 6. Items explored for association with anticipated health behaviours in response to receiving a hypothetical genetic test result indicating higher than average risk for depression. (Maximum N=1046).

Variable	Start therapies				Modify stress				Reduce excessive drug, alcohol use			
	N	Mean (S.D) agreement score	r_s^e/z	p	N	Mean (S.D) agreement score	r_s^e/z	p	N	Mean (S.D) agreement score	r_s^e/z	p
Endorsement of causal attributions[a]												
Genetics	1033	-	0.96	0.156	1011	-	0.15	0.641	870	-	0.01	0.771
Abuse	1033	-	0.11	<0.001[f]	1011	-	0.10	<0.002[f]	870	-	0.07	0.047[f]
Life stress	1033	-	0.13	<0.001[f]	1011	-	0.09	0.006[f]	870	-	0.02	0.578
Family environment	1033	-	0.10	0.002[f]	1011	-	0.05	0.103	870	-	0.05	0.111
Gene-environment interaction	990	-	0.10	<0.001[f]	969	-	0.12	<0.001[f]	834	-	0.09	0.007[f]
History of mental illness												
Self[b]												
Yes	237	4.1 (0.9)	-3.43	0.001[f]	233	4.1 (0.8)	-3.55	<0.001[f]	204	4.1 (0.8)	0.98	0.329
No	794	3.8 (0.9)			775	3.9 (0.8)			665	4.1 (0.8)		
Close relative/friend[c]												
Yes	653	3.9 (0.9)	-0.35	0.728	646	4.0 (0.8)	-0.63	0.53	562	4.1 (0.8)	1.98	0.048[f]
No	372	3.9 (0.9)			358	4.0 (0.8)			301	4.0 (0.8)		
Self-estimation of risk for major depressive disorder[d]												
Higher than average	239	4.1 (0.8)	0.11	0.001[f]	235	4.1 (0.7)	0.11	<0.001[f]	212	4.1 (0.8)		
Same as average	492	3.8 (0.9)			488	3.9 (0.8)			425	4.1 (0.8)		
Lower than average	291	3.8 (1.0)			278	3.9 (0.9)			222	4.2 (0.8)	0.03	0.329
Sex												
Male	401	3.8 (0.9)	-2.12	0.034[f]	392	3.9 (0.8)	-0.72	0.469	354	4.0 (0.9)	2.62	0.009[f]
Female	632	3.9 (0.9)			619	4.0 (0.8)			516	4.2 (0.8)		
Age	1031	-	0.02[e]	0.525	1009	-	-0.01[e]	0.77	868	-	0.03[e]	0.429
Education level												
No post-school education	468	3.9 (0.9)	-0.03	0.98	457	4.0 (0.8)	-0.04	0.7	391	4.0 (0.9)	1.63	0.104
Tertiary education	562	3.9 (0.9)			551	4.0 (0.8)			476	4.0 (0.8)		

[a]Causal attributions of mental illness: range 1 to 5, with higher values indicating greater endorsement. [b]Refers to personal history of a mental illness (depression, bipolar disorder or schizophrenia), [c]Refers to experience of depression, bipolar or schizophrenia through a close relative or close friend. [d]Refers to personal estimation of risk for major depressive disorder compared to average population risk. [e]r_s values are absolute values from Mann Whitney-U tests. r_s values are Spearman's rank correlations. [f]p values <0.1 entered into linear regression
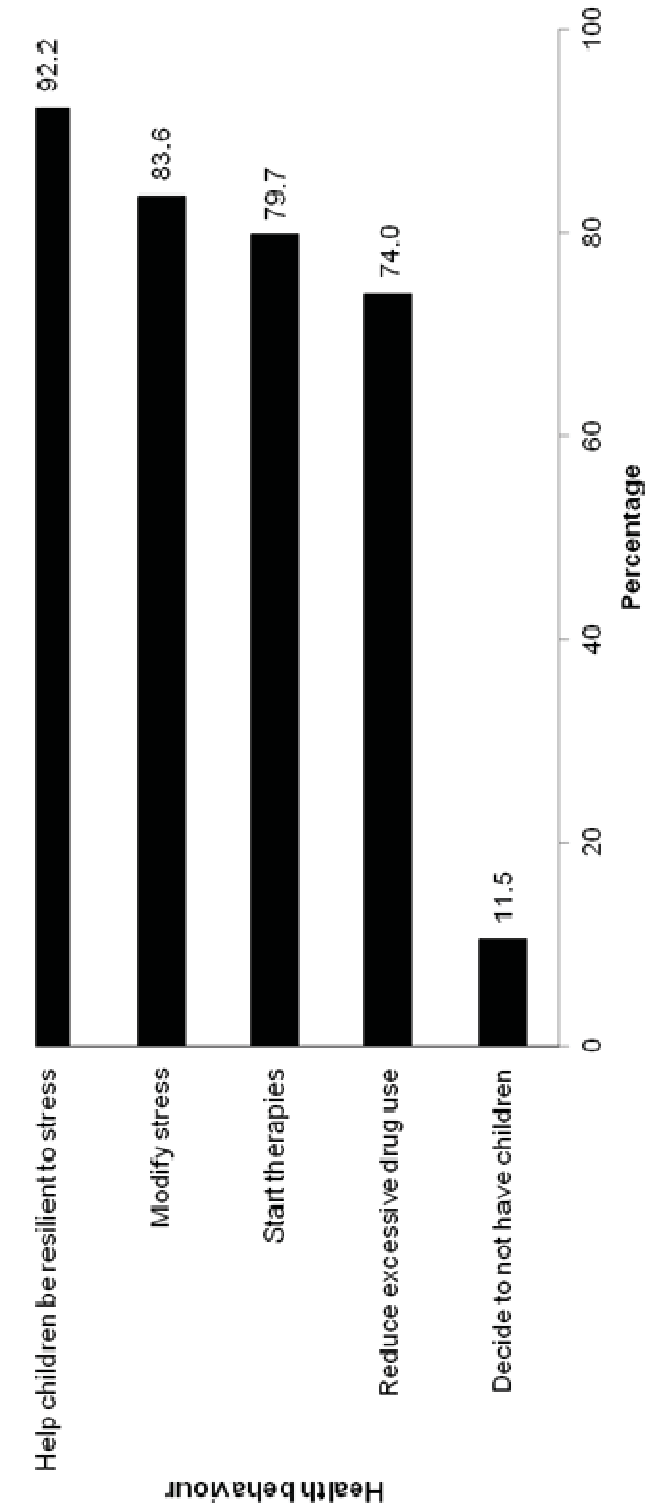
Table 7. Items explored for association with anticipated health behaviours in response to receiving a hypothetical genetic test result indicating higher than average risk for depression (Maximum N=1046).

Variable	Help children be resilient				Decide to not have children			
	N	Mean (S.D) agreement score	r_s^e/z	p	N	Mean (S.D) agreement score	r_s^e/z	p
Endorsement of causal attributions[a]								
Genetics	1007	-	0.01	0.716	816	-	0.05	0.191
Abuse	1007	-	0.10	0.001[f]	816	-	0.26	0.454
Life stress	1007	-	0.03	0.263	816	-	0.10	0.003[f]
Family environment	1007	-	0.03	0.172	816	-	0.05	0.203
Gene-environment interaction	965	-	0.19	<0.001[f]	785	-	-0.01	0.832
History of mental illness								
Personal[a]								
Yes	226	4.4 (0.6)	-3.24		192	2.0 (1.1)	-0.31	
No	780	4.3 (0.7)		0.001[f]	623	2.2 (1.0)		0.002[f]
Close relative/friend[c]								
Yes	645	4.3 (0.7)	-1.24		529	2.0 (1.0)	-2.84	
No	354	4.3 (0.6)		0.217	280	2.3 (1.1)		0.004[f]
Self-estimation of risk for major depressive disorder[d]								
Higher than average	229	4.4 (0.6)	0.10		200	2.1 (1.1)	-0.01	
Same as average	483	4.3 (0.7)		0.001[f]	387	2.1 (1.0)		
Lower than average	286	4.3 (0.7)			223	2.3 (1.0)		0.002[f]
Sex								
Male	392	4.3 (0.7)	-0.71		317	2.2 (1.0)	-1.21	
Female	615	4.4 (0.6)		0.007[f]	499	2.1 (1.0)		0.227
Age	1005		-0.04[e]	0.225	814		0.20[e]	<0.001[f]
Education level								
No post-school education	452	4.3 (0.7)			345	2.3 (1.1)		
Tertiary education	553	4.4 (0.7)	-1.48	0.14	469	2.3 (0.9)	-3.62	<0.001[f]

[a]Causal attributions of mental illness: range 1 to 5, with higher values indicating greater endorsement. [b]Refers to personal history of a mental illness (depression, bipolar disorder or schizophrenia). [c]Refers to experience of depression, bipolar or schizophrenia through a close relative or close friend. [d]Refers to personal estimation of risk for major depressive disorder compared to average population risk. z values are absolute values from Mann Whitney-*U* tests. [e]r_s values are Spearman's rank correlations. [f]p values <0.1 entered into linear regression.

6.3.1   Start therapies or courses

As detailed in the final linear regression model (Table 8), participants willing to start therapies or courses that would facilitate learning of coping strategies in response to receiving a genetic test result indicating increased risk for major depressive disorder were significantly more likely to have estimated their risk for depression to be higher than average ($\beta=0.12$, $p<0.001$); endorse family environment as a causal attribution ($\beta=0.11$, $p<0.001$) and endorse 'gene-environment interaction' as a causal mechanism ($\beta=0.12$, $p<0.001$).

6.3.2   Behaviours to modify life stressors

Participants willing to engage in behaviours that modify life stressors after receiving a genetic test result indicating increased risk for major depressive disorder were significantly more likely to have estimated their risk for depression to be higher than average ($\beta=0.07$, $p=0.029$); endorse 'abuse' as a causal attribution ($\beta= 0.10$, $p=0.003$); and endorse 'gene-environment interaction' as a causal mechanism ($\beta=0.10$, $p=0.002$).

6.3.3   Reduce excessive drug and alcohol use

Participants willing to reduce excessive drug and alcohol use were significantly more likely to be female ($\beta= 0.09$, $p=0.009$).

6.3.4   Help one's own children learn to be more resilient to stress

Participants willing to help one's own children learn to be more resilient to stress were significantly more likely to be female ($\beta=0.07$, $p=0.027$) and endorse gene-environment interaction as a causal mechanism for mental illness ($\beta=0.16$, $P<0.001$).

6.3.5 Decide to not have children

Participants who said they would decide to not have children in response to receiving a genetic test result indicating increased risk for major depressive disorder were significantly more likely to be older (past child bearing age) (ß 0.18, p<0.001), and have a lower level of education (ß = -0.11, p=0.003).

Table 8. Final linear regression models predicting factors influencing intention to take up various behaviours in response to receiving a hypothetical genetic test result indicating higher than average risk for depression, after adjusting for age, sex and education level.

Variable	Raw coefficient	ß	95% CI raw coefficient	t	p
Start therapies or courses[a]					
Self-estimation of risk for major depressive disorder higher than average	0.15	0.12	0.07 to 0.23	3.67	<0.001
Endorse 'family environment' as a causal attribution	0.11	0.11	0.05 to 0.17	3.56	<0.001
Endorse 'gene-environment interaction' as a causal mechanism	0.14	0.12	0.07 to 0.21	3.68	<0.001
Modify stress[b]					
Self-estimation of risk for major depressive disorder higher than average	0.08	0.07	0.01 to 0.15	2.18	0.029
Endorse 'abuse' as causal attribution	0.11	0.10	0.04 to 0.19	2.94	0.003
Endorse 'gene-environment interaction' as a causal mechanism	0.10	0.10	0.04 to 0.17	3.04	0.002
Reduce excessive drug and alcohol use[c]					
Sex	0.15	0.09	0.04 to 0.26	2.63	0.009
Help one's own children learn to be more resilient to stress[d]					
Endorse 'gene-environment interaction' as a causal mechanism	0.14	0.16	0.08 to 0.19	5.15	<0.001
Sex	0.01	0.07	0.01 to 0.18	2.21	0.027
Decide to not have children[e]					
Age	0.01	0.18	0.01 to 0.02	5.15	<0.001
Education level	-0.21	-0.11	-0.35 to -0.07	-3.01	0.003

[a] Final model: R^2 = 0.049, F = 8.405, p <0.001. Adjusted R^2 = 0.044, R = 0. 222. N=976
[b] Final model: R^2 = 0.029, F = 4.655, p <0.001. Adjusted R^2 = 0.022, R = 0.169. N=956
[c] Final model: R^2 = 0.014, F = 4.074, p <0.007. Adjusted R^2 = 0.011, R = 0.118. N=862
[d] Final model: R^2 = 0.034 F = 8.498, p <0.001. Adjusted R^2 = 0.030, R = 0.185. N=950
[e] Final model: R^2 = 0.057, F = 12.146, p <0.001. Adjusted R^2 = 0.052, R = 0.238. N=812

6.4   Discussion

This large population-based study found high acceptance for a range of behavioural interventions to ameliorate risk for major depressive disorder in the hypothetical scenario of receiving a high- genetic risk estimate. Participants who stated an intention to engage in protective health behaviours to reduce risk for major depressive disorder were significantly more likely to perceive a higher than average personal risk for major depressive disorder. This finding supports the value of tailored preventive interventions for target groups with an elevated risk of future depressive episodes who are more likely to be interested in preventive behavioural strategies.

The most frequently rated anticipated health behaviours in response to a hypothetical increased genetic risk for major depressive disorder risk were: helping one's own children learn how to be more resilient to stress (92.2%), modify potential life stressors (82.6%), and start therapies or courses to learn better coping strategies (79.7%). These findings are consistent with previous reports about preferred protective behaviours in response to genetic risk[27, 33] and reported beliefs that such testing could facilitate prevention and earlier intervention of major depressive disorder.[33] Having a personal history of mental illness was not a predictor of willingness to engage in anticipated health behaviours in the final model, in contrast to our first hypothesis. However, perception of having a higher than average risk for major depressive disorder was significantly and positively associated with willingness to start therapies and modify stress, consistent with our second hypothesis. Individuals intending to engage in preventive health behaviours

were significantly more likely to endorse a gene-environment model for major depressive disorder, with endorsement of 'family environment' and 'abuse' as risk factors significantly and positively associated with the intention to take up such behaviours (hypothesis three). This finding suggests that while people may endorse genetics, such individuals may view risk for major depressive disorder as modifiable and may feel that they can 'overcome' a genetic susceptibility with behavioural actions as suggested by Leventhal's Common Sense Model of Self-Regulation.[31]

Few quality randomised controlled trials are available to assess the broader impact of genetic-based disease risk estimates - clinical or hypothetical - on behavioural change. A recent Cochrane review of 17 'poor quality' studies found little evidence that communicating DNA-based disease risk estimates had an effect on smoking and physical activity though there was a possible small effect on self-reported diet and on intentions to change behavior.[34]

Marteau et al[24, 34] argues that genetic information may influence perceptions of which action may be most effective to modify risk rather than influence beliefs that genetic basis makes a disorder less controllable. A study involving predictive genetic testing for the familial hypercholesterolaemia mutation showed that participants with the mutation believed more strongly that a biological-based intervention such as cholesterol-lowering medication would be most effective in reducing cholesterol level and believed less strongly that behavioural change, such as altering diet, would be useful.[24]

Similar results were seen in a small qualitative study on the impact of neonatal genetic screening for familial hypercholesterolaemia, in which parents who perceived the condition as dietary rather than genetic in origin, viewed the condition controllable by altering neonatal diet.[23] Furthermore, provision of a hypothetical genetic test result linked to increased risk of nicotine dependence found that smokers provided with such a genetic test result were more likely to select a pharmacological agent to assist stopping smoking and less likely to select their own willpower, than smokers who were not given such information about genetic risk.[25] These studies demonstrate that perception of origin of risk for disease (genetic or environmental) may influence selection of preventive strategy (biologically-based such as medication, or behavioural-based such as change of diet/smoking habits), as posited by Leventhal.[31] Other studies have shown that rather than facilitating protective behavioural change, genetic risk information could induce fatalistic attitudes, thus inhibiting willingness to engage in protective health behaviors.[23, 24, 29, 30]

By contrast, the present study suggests that genetic risk information is unlikely to demotivate individuals to consider reducing risk through behavioural change, nor induce a sense of genetic fatalism as shown previously.[24,23] Rather, it shows that perceptions that environmental factors contribute to overall risk of major depressive disorder and that these could be controlled by adopting preventive behaviors motivation to modify risk of a hypothetical genetic predisposition to major depressive disorder. The findings may differ from Marteau et al[24] and Senior et al[23] because the previous studies did not attempt to evaluate endorsement of both

genetic and environmental contribution to disease or gene-environment interactions as a perceived mechanism.

The present study found little support for the contention that a hypothetically increased genetic risk for major depressive disorder would lead to the decision to not have children in the event of receiving an unfavourable genetic test result. The minority of participants (10.5%) who said that an increased risk of major depressive disorder would deter them from having children were older and had no post-school education. Previous studies have reported reluctance to have children in the event of having an increased genetic risk of major depressive disorder,[11] bipolar disorder,[4] or schizophrenia [11] among individuals unselected for family history and among individuals with a strong family history of bipolar disorder.[35] Furthermore, overestimation of risk amongst unaffected relatives of individuals with psychosis favoured fewer children.[6] Given the low predictive power and incomplete penetrance of psychiatric genotypes, decisions to not have children based on genetic risk for these disorders may be unjustified. Since genetic risk information also has potential to influence reproductive decisions, further research is required to assess the influence of actual personal genetic risk estimates on reproductive decisions among individuals with a family history of major depressive disorder.

Sex differences were detected in the present study, with females more likely than males to choose to reduce excessive drug and alcohol use and to help children learn resilience as protective behavioral options. The latter finding could be explained by females being more likely to be caregivers to children. Both findings

could reflect the greater likelihood of females to engage in medical interventions generally.[36]

Genetic testing or the provision of personal risk estimates in psychiatry may provide information that can lead to behaviours that promote mental health and reduce risk for disease. The findings do not suggest that provision of genetic risk information directly promotes protective health behaviours, but shows that individuals may be receptive to undertaking protective health behaviours as part of a genetic risk assessment for major depressive disorder.

There is a possibility the hypothetical nature of the genetic risk scenario in the present study weakened participants' sensitivity to the potential personal impact of such a genetic risk. It should be noted that evidence thus far for the impact of clinical or hypothetical risk estimates on promoting behavioural change is based on small trials or hypothetical risk estimates. Large randomised control trials are required using risk estimates based on personal hereditary risk information and individual environmental risk factors to determine the extent to which individual risk influences perception of how risk for a major depressive disorder might be controlled and motivation to adopt health behaviours that ameliorate that risk.

This is the first study to provide data from a large national cohort in which motivation to change health behaviour in response to hypothetical depression genetic risk testing has been investigated. It is likely that how strongly particular risk factors for mental illness are endorsed may influence perceptions about what kind of interventions might be effective in reducing risk or preventing disease. The

results suggest that informing people of their genetic susceptibility to disease may motivate risk-reducing behaviour, although this may not occur as a direct result of genetic testing. In particular, the study has identified that individuals who perceive themselves to have a higher than average risk for major depressive disorder who endorse the contribution of genetic and environmental risk factors to the development of the illness are likely to be motivated to engage in various protective interventions at a pre-symptomatic stage. The study has shown that mental health interventions that facilitate learning of effective coping skills are likely to be well-received as preventive strategies.

These findings now require investigation in a prospective study to evaluate how the impact of actual individual risk estimates for major depressive disorder may differ from the hypothetical scenario posited in this study. Studies are required to investigate the uptake of cognitive and behavioural protective strategies following the provision of actual risk estimates, based on genetic and non-genetic risk factors, to inform the design and planning of primary prevention of major depressive disorder in healthy people in high-risk groups.

6.4.1   Limitations

There is a possibility the hypothetical nature of the genetic risk scenario in the present study weakened participants' sensitivity to the potential personal impact of such a genetic test result. It is possible that by asking participants to consider their responses in terms of depression, bipolar disorder, and schizophrenia initially could have confounded the later answers that focused specifically on depression. However, including bipolar disorder and schizophrenia in addition to depression in questions about stigma (chapter 5) and causal attributions (chapter 6) provides a good basis upon which to evaluate public attitudes towards psychiatric genetics in

general. Survey methods as employed by this research have limited power to predict future human behaviour. This should be considered when interpreting the findings. While the study aimed to set the questions to participants at reading level year 8, the study did not use measures to ensure all participants understood the genetic terms used. This may limit interpretation of data.

6.5   Conclusions

This is the first study to provide data from a large national cohort in which motivation to change health behaviour in response to hypothetical serotonin transporter genotyping has been investigated. The results suggest that informing people of their genetic susceptibility to disease may motivate them to change their behaviour to reduce their risks, although this may not occur as a direct result of genetic testing. In particular, the study has identified that individuals who perceive themselves to be at increased risk for major depressive disorder and who endorse gene-environment interactions as a cause are likely to be motivated to engage in various protective interventions at a pre-symptomatic stage. The study has shown that mental health interventions that facilitate learning of effective coping skills are likely to be well-received as preventive strategies by such groups.

Prospective studies are needed to evaluate how the impact of actual risk estimates may differ from the hypothetical scenario posited in this chapter. Further studies should use actual risk estimates based on genetic or hereditary risk information to determine the extent to which individual risk influences motivation to adopt health behaviours that ameliorate risk for major depressive disorder and perception of which preventive strategies might be most effective.

6.6   References

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7   STUDY 3.

Portrayals of psychiatric genetics in Australian print news media
1996-2009

7.1   Introduction

The mass media are a key source of health and science information for the lay
public.[1-5] Historically, public sources of such information has come from mass-
circulation of newspapers and magazines as well as broadcast media. With the
advent of internet technology and subsequent decline of newspaper readership, a
major source of medical and scientific information is likely to be derived from
digital media, especially amongst young people.

Medical genetics has received substantial coverage in the international media over
the past few decades, with greater intensity of coverage appearing to coincide with
announcements of discoveries of new susceptibility genes.[2] Media discourse about
genetics and mental illness has been negligible.[6]

Medical issues that receive intense coverage in the media gain a key position in
public and political discourse.[7, 8] The media set a news agenda by emphasising
certain aspects of a health issue (such as issues that attract readers, listeners or
advertisers) while minimising or ignoring other issues (such as negative results of
scientific studies). Journalists have the opportunity to push an issue higher up the
news agenda by framing an issue through their choice of angle, sources interviewed
and quotes selected. Scientists also contribute to news framing by pushing particular
aspects of scientific findings or omitting to mention negative results.

Thus, the media has strong influence on what becomes 'news' which shapes
knowledge, beliefs, values[9] and public opinion,[2, 10] while is also itself influenced by

public discourse.[10] Thus the science and health news agenda has implications for public discourse, health care, policy and public uptake of new technologies. Analysis of news frames about mental illness and genetics provides an opportunity to systematically determine how the media is likely to influence public and political discourse.[11]

Previous media analyses of genetic news items identified genetic determinism,[10, 12, 13] genetic optimism[2] and genetic pessimism[2] as important agenda-setting frames. Deterministic framing portrays genes as the cause of disease and has the potential to overstate the role of genes in mental disorders and contribute to stigma associated with mental illness.[10,14] The genetic optimism frame promises an positive impact of the role of genetic technologies in mental illness and may offer false hope about the effectiveness and availability of molecular-based treatments.[2] The genetic pessimism frame presents a genetic dystopia where 'inferior' DNA is perceived to doom individuals to a genetic underclass as depicted in popular culture such as seen in Aldous Huxley's *Brave New World* and the movie *Gattaca*.

Although believed to be pervasive in the media,[10,14] genetic determinism is reported to have decreased in US news media, with a significant decrease in the number of articles assigning genetic causes to mental and behavioural characteristics.[6] Genetic optimism, by contrast, is reported to be dominant in the US media,[2, 15,16] and has persisted in the media even after subsequent failure to replicate reported genetic-disease associations.[2]

The present study aimed to qualitatively analyse news articles about the role of genes in depression, bipolar disorder and schizophrenia in the Australian print media, by mapping the use of the frames of genetic determinism, genetic optimism and genetic pessimism. The study hypothesised that i) probabilistic risk framing would be more prevalent than deterministic framing, and that ii) the frame of genetic optimism would be used more frequently that of genetic pessimism.

7.2   Materials and Methods

Relevant newspaper articles were systematically identified on the Dow Jones Interactive database (Factiva) via date-limited keyword searches from 1 January 1996 to 31 Dec 2006 and later updated to 31 Dec 2009, using the keyword formula (depression or bipolar or (manic depression) or schizophrenia) and (gene or genes or genet* or DNA) or (DTC or "direct to consumer").

News stories were examined using content[17, 18] and frame analysis.[11] After removal of articles meeting exclusion criteria (duplicates, off-topic articles and articles only briefly mentioning psychiatric genetics), items were judged to be eligible for analysis and studied for relevant content. Criteria for eligibility were articles that mentioned major depressive disorder, bipolar disorder or schizophrenia in relation to: causal attributions; genes, genetic risk, or genetic technology; or diagnosis, management or treatment involving genetic risk information or family history.

7.2.1   Content analysis

Content analysis is specifically designed to enable systematic objective evaluation of messages in the mass media. Underpinning content analysis is intercoder or interrater reliability, also termed intercoder agreement, a mathematical measure that determines the extent to which independent judges reach the same conclusion about characteristics of messages in the media,[19] and whether the analysis based on qualitative judgment-coded data can be relied upon. A standardised approach to methodology in content analysis is therefore critically important.

Intercoder reliability

How intercoder reliability should be measured is contentious. Indices range from liberal, e.g. per cent agreement, to conservative, e.g. Krippendorff's α (alpha), Scott's π (pi) and Cohen's κ (kappa) and others. Per cent agreement has been highly criticised because it does not correct for agreement by chance.[20] Cohen's kappa, designed for assessing reliability of agreement between two coders, is reported to be

the most widely used reliability coefficient in content analysis.[21] Cohen's kappa is chance-corrected and assumes both coders have coded all units.

A further point of contention is how intercoder reliability coefficients should be interpreted in terms of critical value. Kripendorff defines critical value as an acceptable level of agreement below which the data should be rejected.[22] Solutions proposed include the use of coefficients on a liberal to conservative continuum or the acceptance of a higher critical value for liberal indices (e.g. 0.9) and lower critical value for rigorous or more conservative indices (e.g. 0.7).[19]

Krippendorff[22] criticises claims that lower critical values should be acceptable when the results of a content analysis are intended to support scholarly arguments (e.g. minimum $\alpha \geq 0.667$) but should be higher when the outcome of the content analysis has implications for human survival (e.g. minimum $\alpha \geq 0.8$)

7.2.2   Frame analysis

The author developed a conceptually clustered coding tree according to widely accepted standards of qualitative methodology.[23] Whole articles were assigned codes for publication, year of publication and psychiatric disorder(s). A second coder (a research psychologist) informally recoded ten percent of the sample to identify any discrepancies in interpretation of codes. The coding instrument was then refined by merging, deleting, or inserting codes, and revising coding descriptions until the informal assessment suggested an adequate level of agreement by consensus.[19]

A third coder (a senior lecturer in media studies and medical writer) was trained in the coding instrument, and double-coded ten per cent of the sample, to allow for a formal intercoder reliability assessment. This coding was performed independently and without consultation or guidance. Cohen's kappa was used to calculate interrater reliability,[19, 24] which yielded a kappa coefficient of k=0.68 (S.D= 0.25), representing good agreement beyond chance for a 26-item coding tree.[25]

The author then coded all transcripts by paragraph[2, 9, 2, 11, 17] using 26 content and framing codes shown in Appendix C.1. Descriptors of codes are shown in Appendix C.2.

Coded articles were subsequently analysed for existing and emergent frames with the assistance of the software package QSR N6,[26] to assist with the organisational aspect of coding, and according to the methods described by Miles and Huberman (1994).[27] This facilitated comparisons between articles from different publications and years as well as other aspects of the analysis. The conceptual approaches of Entman (1993)[11] and Scheufele (1999)[17] were used to guide the framing analysis.

7.3   Results

The systematic database search resulted in the retrieval of 3,623 news items. Removal of exclusions resulted in a final sample of 406 news items across 14 Australian news publications from 1996 to 2009 (Figure 4).

Figure 4. Extent of coverage of psychiatric genetics in the news media by publication 1996-2009 (N=406).
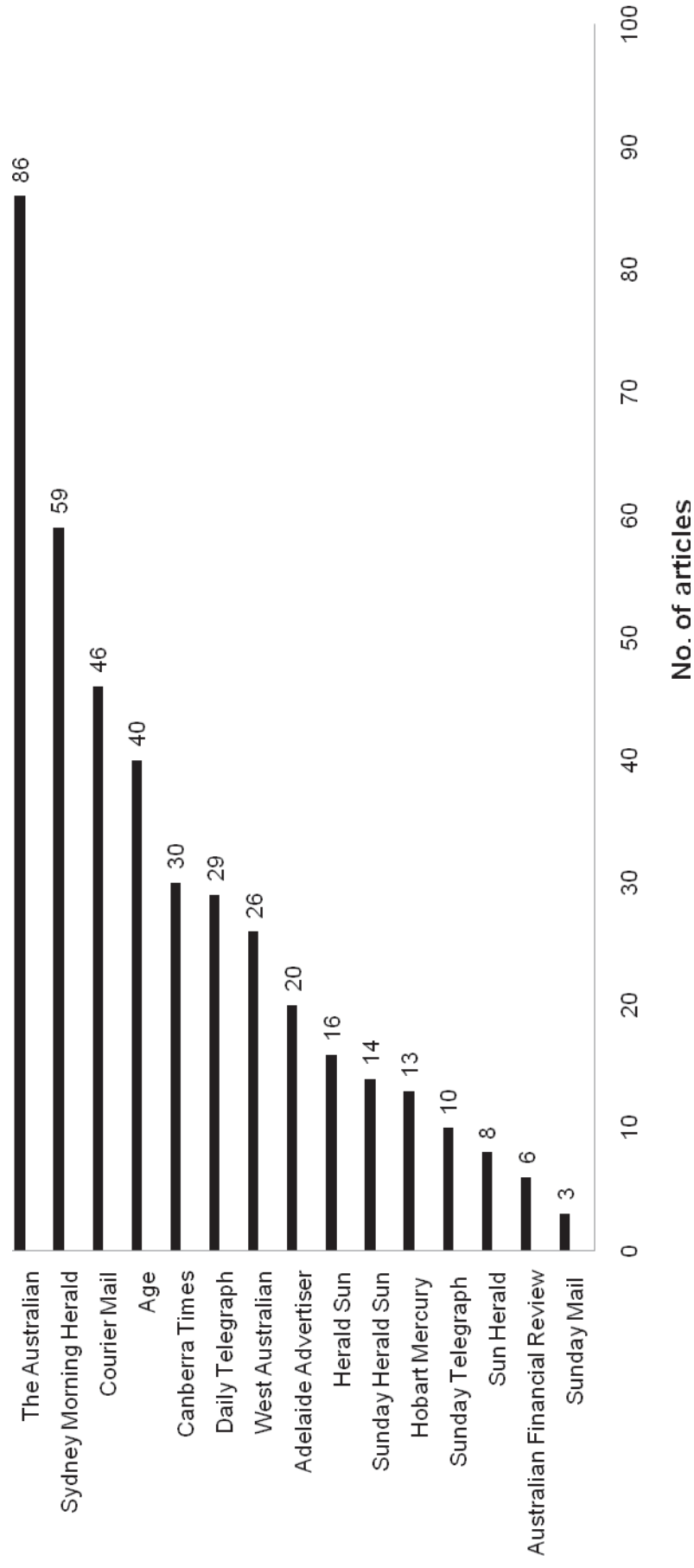
Figure 5 shows the number of items about psychiatric genetics increased steadily over the 14 year period, with more than 50% of items published since 2007. In relation to genetics and mental illness, depression featured the most frequently in the sample (199/406 items, 43%), followed by schizophrenia (181/406 items, 26%) and bipolar disorder or 'manic depression' (83/406 items, 17%) with some items including more than one of the three target disorders.

Figure 5. Coverage of psychiatric genetics in the Australian news media by year (N=406)
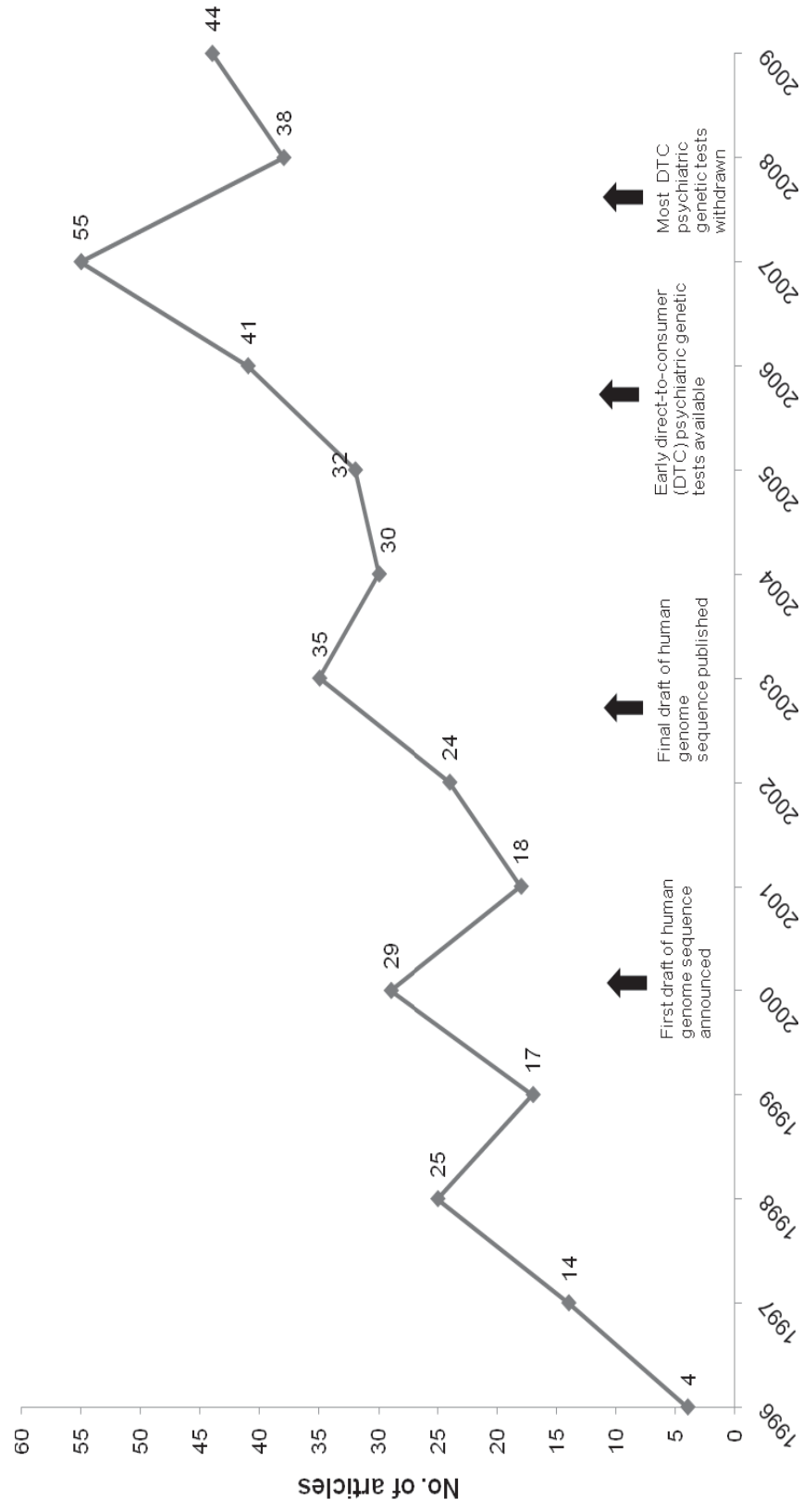
7.3.1 Causal attribution

Content analysis revealed that causal attribution of mental illness (354/406 items, 87%) was a dominant theme. Figure 6 shows the dominant discourse about the aetiology of depression, bipolar disorder and schizophrenia focused on the interaction between genetic and environmental risk factors (179/354, 50%).

G X E interactions (179/354 items; 44%) tended to be framed as a genetic predisposition with environmental factors acting as triggers:

> *"If you want to know if you have a genetic disposition to schizophrenia or other mental illness, indulge in cannabis because it will trigger it." 2/2/2001, The Age News, p.6.*

Of the 70 items (70/354; 20%) that attributed environmental factors alone to the aetiology of mental illness, stressful life events (17/70; 24%) were presented as the dominant factor:

> *"The biggest category of cause [of depression] is probably a life experience such as the death of a loved one, loss of a job or repeated bullying." 4/3/2006, Hobart Mercury.*

Twenty-two other environmental causal attributions identified in the media were bereavement, job loss, financial strain, "the global financial crisis", victim of crime, bullying, natural disaster, lack of social support, viruses, child abuse/neglect, poverty, drug and alcohol use, co-morbidities, insomnia, coping styles, uterine environment, parental age at conception, post-natal adjustment disorders, family environment, trauma, virtual stalking and "contemporary society."

Figure 6. Media framing of genetics, mental illness and its causes 1996-2009 (N=406).
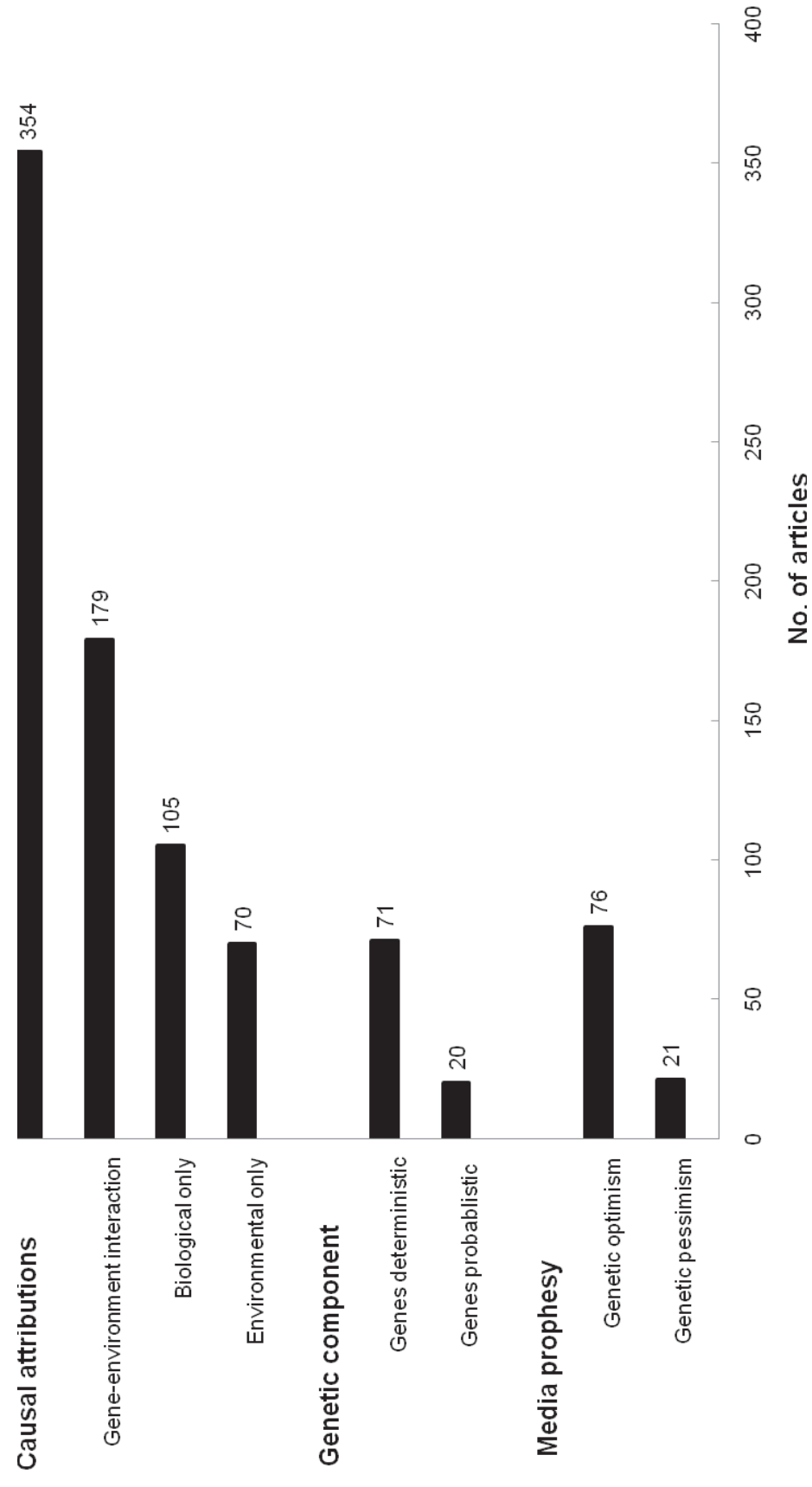
7.3.2   Genetic determinism

Of the 91 items (91/406; 22%) that carried messages about the role of genes in the development of mental illness, genetic determinism (71/91; 78%) was the dominant frame.

> *"In a world first, researchers from NSW have discovered the gene responsible for depression." (26/2/2006, Sunday Telegraph, p3.)*

Twenty items (20/91; 22%) framed the role of genes as probabilistic rather than deterministic:

> *"…having a genetic predisposition to …[depression] did not mean it was expressed." (8/10/1999, Herald Sun, p24.)*

Contrary to the first hypothesis, the frequency of reports using deterministic framing (78%, 95%CI 68% to 87%) was significantly greater than that of reports that used probabilistic framing (22%, 95%CI 3% to 31%).

7.3.3   Genetic optimism and pessimism

Ninety-seven items (97/406; 24%) used optimistic or pessimistic frames. Of 97 items, common optimistic discourse (76/97; 78%) used the terms "*hope*", "*world first*" and "*breakthrough*", and often alluded to positive impact of genetic discoveries on future treatment options:

> *"For the first time, researchers have hard evidence that genetic mutations in the immune system are linked to schizophrenia … the findings provide hope of better treatment for the devastating psychiatric disorder …" (2/7/2009, The Australian, p7.)*

Pessimistic discourse (21/97; 22%) about genes and mental illness focused on the negative impact of labelling, negative political agenda, the prospect of a "genetic underclass", increase of stigma and/or risk of eugenics:

> "*Genetic testing [for a mental illness] seems certain to allow doctors to predict which diseases patients are likely to develop years before they show symptoms - raising the prospect of a 'genetic underclass'. (13/2/2001, The Advertiser (Adelaide), p3.)*"

Frames of genetic optimism (78%, 95%CI 68% to 87%) were used significantly more frequently than frames of genetic pessimism (22%, 95%CI 4% to 31%), confirming hypothesis two.

7.3.4   Ethical and social implications of psychiatric genetics

Discourse about psychosocial and ethical implications of psychiatric genetics occurred in 95 of 406 items (23%). Discourses included stigma, threat to privacy of genetic information, equity of access to genetic services, eugenics, genetic discrimination by employers and insurance companies, the right to know or not to know one's genetic information, impact of genetic testing for risk of psychiatric disorders on relatives and risk of distress after receiving one's genetic test result.

7.3.5   Perceived medical benefits of psychiatric genetics

Content analysis revealed 175 of 406 items (43%) reported potential clinical applications of genetic research in psychiatry. The six applications were about preventive interventions (50/175; 32%); pharmacogenetics (49/175; 32%); genetic susceptibility testing (44/175; 28%); gene therapy (13/175; 8%); improved treatments and technology (11/175; 7%) and personalised medicine (8/175; 5%). Of the 97 items that framed such clinical outcomes as positive or negative, the predominant frame was genetic optimism (76/97; 78%).

"If people know that they have a genetic susceptibility it may become possible to avoid episodes of mania or depression by monitoring and treating early changes in brain chemistry, or by trying to reduce environmental triggers, such as stress…" (11/9/2003, Sydney Morning Herald, p3.)

7.3.6 Genetic prophesy

This investigation identified the frame of 'genetic prophesy', which occurred 24 times in the sample. The frame consisted of prophesies about when molecular-based interventions will become available, usually with specific and finite time frames. Table 9 shows that predictions predominantly focused on future identification of genes involved in psychiatric disorders (9/24; 38%), introduction of genetic susceptibility tests (7/24; 29%), genetic-based insurance evaluation (1/24:4%), pre-natal genetic diagnosis for depression or schizophrenia (2/24;8%), availability of low cost personal genome sequencing and future pharmacogenetic services (3/24; 13%). A total of 20 scientific advances were predicted to occur by the present day (2010). The majority of these (87%) failed to manifest. Two items accurately predicted in 1998 and 2001 respectively that genetic tests or genome sequencing involving psychiatric disorders would be available by 2010, although these commercial genetic test are based on unreplicated findings.

Table 9. Media predications 1996-2009 about outcomes of psychiatric genetics research.

Prediction	Year predicted	Year promised	Outcome of prediction[a]	Publication
"A test to pinpoint the genes indicating schizophrenia is not far away."	1996	"Not far away"	Some genetic studies show associations, but clinical validity and utility still unclear by 2010.	*The Age*
"They hope to identify the gene - there is probably only one in the region - which contributes to the…[bipolar] illness within 18 months."	1998	2000	Some genetic studies show associations, but clinical validity and utility still unclear by 2010.	*The Australian*
"…There will, in the next 10 to 15 years, be a whole range of these susceptibility genes that are identified for many of the common diseases …which will include …depression,…"	1998	2008-2013	Depression susceptibility gene replicated 2003-2009 follwed by positive and negative meta-analyses. Commercial 'whole genome' scanning became available DTC by 2007 for 23 polymorphisms based on unreplicated findings.	*Sydney Morning Herald*
"…the genes which cause …schizophrenia might be identified within three to five years."	2000	2003-2005	No causal genes identified by 2010.	*Courier Mail*
"I fear that over a five or 10-year period some new companies will set up, offering life insurance based on genetic evaluation…"	2000	2005-2010	Did not happen by 2010.	*The Australian*

Table 9 cont.

Prediction	Year predicted	Year promised	Outcome of prediction[a]	Publication
"The head of the Human Genome Project, Francis Collins, predicts that it will take up to seven years to locate the genes that cause…manic depression."	2000	2007	No causal genes identified by 2010.	*The Age*
"…it may be possible for a pregnant woman to know categorically that her unborn child possesses genes conferring a predisposition to…depression…"	2000	2003-2004	Did not happen by 2010.	*Canberra Times*
"Genetic make-up of schizophrenia"	2000	"Short-term"	Still much unknown.	*Daily Telegraph*
"Creation of a successful test …[suicide prediction associated with anti-depressant] may lead to more careful treatment of depressed patients who carry the mutation."	2000	2002	Not clinically available by 2010. Commercial test available direct-to-consumer (DTC) in 2007 based on unreplicated findings, withdrawn in 2008.	*Sunday Herald Sun*
"Predictive genetic tests for dozens of diseases"	2001	2010	DTC 'whole genome' scanning became available DTC by 2007. Several commercial 'genome scanning' service were operating in 2010.	*Adelaide Advertiser*

Table 9 cont.

Prediction	Year predicted	Year promised	Outcome of prediction[a]	Publication
"…within five to 10 years we will have very "solid knowledge" of how genes interact with environment to cause mental illness."	2002	2007-2011	Still much unknown by 2010.	*The Age*
"…a simple genetic test to become available to check if males from families with a history of males-only bipolar disorder have an XBP1 gene mutation."	2003	"Expected"	Did not happen by 2010.	*Sunday Herald Sun*
"Only a day after the announcement scientists had discovered a gene that makes people susceptible to schizophrenia, patients were already asking their doctors to be tested for the hereditary condition…."	2003	"May never be [available]"	Not clinically available by 2010.	*The Australian*
"Schizophrenia genes found. The drugs could be expected on the market within six to eight years."	2004	2010-2012	Treatments based on gene discovery unavailable by 2010.	*Hobart Mercury*
"… predict gene tests for predisposition to… schizophrenia, depression … will also be on offer in five to 10 years.	2004	2009-2014	Not clinically available by by 2010.	*Herald Sun*
"Twenty-minute genetic tests leading to better medication prescriptions for schizophrenia"	2005	2007/2008	Did not happen by 2010.	*Courier Mail*
"Isolation of major schizophrenia gene announced"	2005	2005	Not robustly replicated by 2010.	*Courier Mail*

Table 9 cont.

Prediction	Year predicted	Year promised	Outcome of prediction[a]	Publication
"…my hope is within the next five years…we will have identified the first true gene for schizophrenia."	2005	2010	No "true gene" identified by 2010. Genetic studies show some associations, clinical validity and utility unclear.	*Daily Telegraph*
"Identify genes which play a role in the development of schizophrenia"	2005	2010	Some associations identified by 2010, but clinical validity and utility unclear.	*Courier Mail*
"Within a decade, it is predicted, the cost will drop far enough for everyone to have their own genetic code sequenced."	2007	2017	By 2010, 23 gene-disease association 'scans' werer available for around US$399but clinical validity and utility in question.	*Sydney Morning Herald*
"…we may be, in five or 10 years' time, in a situation with schizophrenia that cervical cancer is now in."	2006	2011-2016	Unavailable by 2010. "20 years ago most experts believed psychotic disorders such as schizophrenia would be understood in a decade."	*Sydney Morning Herald*
"… it would be premature to develop genetic tests for a predisposition to schizophrenia based on the findings because they did not account for all cases of the disease."	2008	Not promised: "Premature"	Unavailable by 2010	*Sydney Morning Herald*

Table 9 cont.

Prediction	Year predicted	Year promised	Outcome of prediction[a]	Publication
"…it is too soon to gene test individuals as much of the genetic puzzle is still missing, but the find provides powerful insight into the type of mutations to look for."	2008	Not promised: "Too soon"	Unavailable by 2010.	*Hobart Mercury*
"…ability to diagnose unborn babies at risk of complex disorders such as schizophrenia…will be possible before the turn of the next century."	2009	2100	Unavailable by 2010.	*Courier Mail*

[a]'Outcome of prediction' is based on the authoritative review Mitchell et al, Predictive and diagnostic genetic testing in psychiatry. *Psychiatric Clinics of North America.* 2010; 33(1):225-243.

7.4   Discussion

This is the first systematic analysis of Australian news depictions of psychiatric genetics. The rapid rise in quantity of media coverage about genetic advances in psychiatry since 1996 suggests the subject is gaining increasing importance on public and political agendas. Peaks in coverage appeared to coincide with the announcement of the publication of the first and final drafts of the human genome sequence in 2000 and 2003. The largest peak coincided with the upsurge of direct-to-consumer genetic tests for risk of mental disorders during 2007-8. This is consistent with previous observations that news coverage about genetic advances in medicine intensifies at times of significant scientific announcements.[2]

The study found that the media appear to predominantly portray mental illness as resulting from the interaction of genetic and environmental factors. It identified conflicting messages about the power of the genetic component, which was portrayed more frequently as deterministic rather than probabilistic, in contrast to hypothesis one. This suggests that the public may be misinformed about the complexities of the genetic underpinnings of mental illness and the interaction with the environment.

Caspi et al[28] warned that deterministic beliefs, whether environmental or genetic, could lead to poorly conceived mental health initiatives and at worst, promote policies that violate human rights. They argue that media portrayals of environmental effects on gene expression as a model for mental illness will enhance public understanding of the causes of behaviour. According to Caspi et al, the key to that understanding will be an acceptance that behaviour as an outcome of gene expression is in part influenced by lifestyle choices which are under human control, which will be a strong defence against the misuse of genetic information.[28]

It has been argued that shortening of complex genetic concepts into brief attention-grabbing headlines might contribute to a deterministic framing effect in the media, although one study found no evidence of this.[14] Furthermore, the need for editorial

brevity can pressure journalists to transform complex concepts about genetic penetrance in multifactorial disorders into shorter more accessible deterministic statements. The findings contradict earlier research, which found news reports rarely mentioned the influence of non-genetic risk factors for mental disorders.[9]

The optimism frame in the present study predominantly described utopian expectations of molecular-based future treatment for psychiatric disorders, in particular, preventive interventions, pharmacogenetics and genetic susceptibility testing. It is believed that the agenda underpinning positive images about the clinical benefits of genetic research is set not only by editors and journalists who view items about the potential to solve health problems as highly newsworthy, but also by some scientists employed in the biotechnology industry who may seek to boost public expectations about treatments, hoping to assure continuation of funding for their research.[9] Negative images of genetic research, such as reports of regular failures to replicate genetic associations with certain diseases,[2] and items with negative messages about eugenics were less frequently used than the genetic optimism frame, which supports hypothesis two.

Consistent with previous research, the study found a high prevalence of overpromising of future availability of perceived medical benefits from psychiatric genetic research.[2, 9] Twenty of 24 predictions did not manifest by the predicted date. Predictions focused on the future discovery of genes associated with mental illness. While many associations have been identified by the predicted date, in particular the reported replication of *5-HTTLPR*, clinical validity of many of these associations had not been determined, nor become clinically available. Several predictions about the availability of "predictive genetic tests for dozens of diseases" were the most prophetic, as numerous DTC genetic tests have become available since 2007 via unregulated commercial services. What the media did not predict was the controversy that such genetic testing services would generate, including legislation reform and subsequent bans on the marketing of DTC genetic tests in some countries.[29]

Failures to replicate previously published genetic associations with psychiatric disorders are rarely reported in the media,[2] yet optimistic predictions about medical

benefits persist. This is likely to reflect an inclination for journalists to cover news from high impact journals, which tend not to publish negative studies. Furthermore, there is a tendency for the media, influenced by professional norms such as news values, to publish only positive results from genetic studies, resulting in a publication bias.[16, 30] Since the news media are a major source of public understanding of genetics, optimistic framing may distort public understanding of the influence of genes in multifactorial disease and future options for preventing, treating and managing mental illness.

Based on figures[31] available at the time of the analysis of newspapers included in the sample, total circulation (15 publications) was 7,412,865. This suggests an estimated total average readership of 22,238,595 per issue (15 publications). These figures do not account for international and online readers. The data suggest that the content examined in this study had potential to reach a large audience, although it cannot be assumed that every article examined in the analysis was read by every reader, nor can the impact of the content on that audience be surmised.

There was a relatively low media profile of social and ethical issues in the sample. The most frequent ethical discourses in the present study were the potential for genetic discrimination among employers or insurance companies and the potential for evidence of a genetic component in mental illness to increase stigma. Marginalisation of these issues suggests social and ethical discourse about psychiatric genetics is low on the public and political agenda, which could potentially have negative consequences for individuals affected by depression, bipolar disorder or schizophrenia. The media analysis has revealed a clear example of media agenda setting by demonstrating that topics about media-predicted outcomes of psychiatric genetic research are clearly heightened and at times exaggerated, while topics about social, ethical and legal implications are marginalised.

7.4.1 Limitations

A limitation of the study is that the analysis only covered print news articles. While there appears to be a strong association between news coverage in newspapers and digital news media[32] the present study may have underestimated total news coverage of the topic. The decline of print readership may pose a limitation to the study. However it should be noted that a substantial proportion of Australian print news is available from digital media outlets, in particular Fairfax digital and news interactive, the online audiences of which are substantially from younger demographics.[33] Other media formats and outlets should be considered before conclusions are made about the full spectrum of media representation of psychiatric genetics.

Contrary to recommendations[18] the third (formal) coder was not 'blind' to the purpose of the study and the research question guiding the investigation. This was unavoidable given the complexity of the coding tree, and the necessity that this coder should fully understand the variables and their descriptors.

7.5 Conclusions

A high level of media coverage of psychiatric genetics suggests the public endorses genetic research in psychiatry and potential mental health benefits. Optimistic portrayals of how genetic information might be used for mental health promotion match community interest in and attitudes towards psychiatric genetics reported by the studies in the previous chapters of this thesis. The present study has revealed a lack of balance between perceived positive outcomes of psychiatric genetic research and critical commentaries about potential ethical and social implications. Optimistic predictions about the use of genetic information in psychiatry could encourage unrealistic public expectations about how future mental health problems might be solved. Further research should include television and internet media portrayals of psychiatric genetics, especially as audiences of such media are likely to be a younger demographic who are likely to be most interested in genetic susceptibility

for depression. Studies that assess the impact of media portrayal of psychiatric genetics on audiences would be valuable.

7.6 References

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8 THE FUTURE OF USE OF GENETIC RISK INFORMATION IN PSYCHIATRY

8.1 Using genetic risk information to inform preventive interventions

The broad aim of this thesis has been to document psychosocial implications of genetic risk information about psychiatric disorders by evaluating both public response to hypothetical genetic susceptibility testing for risk of major depressive disorder and motivation of healthy people to engage in preventive interventions based on genetic susceptibility. This issue has become increasingly pertinent since advances in genetic studies, and genome-wide association studies in particular, have enabled identification of common genetic variants and mutations reported to be associated with a number of psychiatric disorders. As a result of these developments, there has been an international surge in unregulated DTC genetic susceptibility testing predominantly available via the websites of commercial biotechnology companies. Thus, the need for research into psychosocial and clinical implications of genetic risk information about psychiatric disorders has become urgent.

Over the duration of the studies of this thesis there has been a steady increase in speculative debate about the public health implications of genetic susceptibility testing across the health spectrum. In particular, the advent of DTC genetic testing has attracted concern, leading to the commencement of government consultations in many countries to determine how such tests should be regulated and how consumers should be protected. Current unresolved issues addressed by this thesis include the evaluation of public interest in genetic susceptibility testing and attitudes towards the use of genetic risk information in psychiatry. The thesis has also addressed and

how public understanding of the aetiology of psychiatric disorders might affect uptake of molecular-based preventive mental health interventions. It has also investigated public perception of potential genetic discrimination, privacy issues, ethical implications and potential stigma resulting from genetic risk information about psychiatric disorders. Finally, the thesis discusses how genetic risk information should be used in preventive health care. This thesis also fills a gap in the research into media portrayal of psychiatric genetics to enable insights into how these issues are positioned on the public and political agenda.

Public attitudes towards psychiatric genetics and implications of genetic testing were examined. Qualitative analyses were undertaken to explore the range of views of the public and quantitative analyses, using a survey methodology involving a random sample of the general population, was performed to explore the extent of community attitudes. The media analysis used content and framing analyses to examine the portrayal of psychiatric genetics, genetic testing and its psychosocial and ethical implications in a structured sample of news items published in Australian newspapers over a 14-year period.

8.2   Key findings of this thesis

This thesis has demonstrated that the community is highly receptive to, and interested in, genetic susceptibility testing for risk of major depressive disorder. The preferred mode of access of genetic susceptibility testing appears to be through clinical services, with some interest in DTC genetic testing. A genetic explanation for major depressive disorder may exacerbate stigma associated with this disorder. Healthy individuals are prepared to modify a genetic predisposition for major depressive disorder at a pre-symptomatic stage through preventive behaviours, although perceived modifiability of environmental risk factors is variable. Current optimistic print media portrayals of potential clinical utility of genetic information about mental illness may encourage unrealistic expectations about the future use of psychiatric genetics in health care.

This chapter will provide an overview of the empirical studies contained in this thesis, a summary of the major findings and a discussion of the implications of the findings for the future of genetic susceptibility testing in psychiatry. Limitations of the studies are discussed with suggestions for improving the validity of the data. The chapter concludes with a research agenda that aims to inform future genetic testing services or future preventive interventions for people at high risk of major depressive disorders based on risk estimates for mood disorders.

8.3 Rationale

This thesis commenced with a qualitative study to identify the range of beliefs about genetic risk information and anticipated health behaviours rather than the extent to which participants held particular beliefs. This presented an opportunity for new insights into the topic and new lines of inquiry which provided an appropriate basis from which to inform the design of the population survey for the quantitative stage of the thesis. The quantitative study provided empirical data with which to assess representativeness of beliefs from both parts of the qualitative studies in the general population. Data on community beliefs and understandings about psychiatric genetics and endorsement of health behaviours provided by the quantitative study may be used to inform education initiatives and future mental health interventions using genetic technologies. Such beliefs are likely to be shaped by media portrayal of causal models of mental illness and framing of the clinical utility of genetic information about mental illness. Thus, analysis of media portrayals of psychiatric genetics provided an understanding of how public discourse on these issues is being shaped and how this might impact on the integration of genetic technologies in future preventive interventions in psychiatry.

8.4 Overview of findings from the empirical studies

8.4.1 How acceptable is genetic susceptibility testing to the community, using depression risk genotyping as an example?

Individuals accessing genetic susceptibility tests, whether through a clinic or DTC, face positive and negative implications associated with the test results. Implications associated with genetic test results for multifactorial disorders are complicated by the uncertain clinical validity of the tests and incomplete penetrance of the mutations involved, and thus uncertain risk estimation. Data on community acceptance of genetic susceptibility tests for risk alleles or mutations associated with increased risk for psychiatric disorders to the public is needed to inform the design of future genetic testing services and assist psychiatrists, general practitioners, genetic counsellors and clinical geneticists to determine information needs for their patients.

The qualitative study found positive public attitudes towards genetic testing for susceptibility to major depressive disorder, if it were available. Interest in hypothetical genetic testing for risk of major depressive disorder was sustained despite an understanding that the result offered a probabilistic rather than a definitive risk. Beliefs prevailed that evidence of a genetic component would validate depression as a biological medical condition. The study found perceptions that genetic testing for depression risk could offer scope for early intervention by forewarning individuals with an increased risk to seek early professional help, as well as prompting people to learn techniques that might minimise or prevent the development or severity of depression. Concerns about perceived discrimination by insurers or employers and perceived threat to privacy modified interest in genetic susceptibility testing. Other concerns included the prompting of fatalistic thinking in the event of having an high risk result, lack of definitive risk estimate and that no related preventive interventions are currently available. Interest among individuals who did not have a personal or family history of depression (unaffected) varied according to certain conditions being met. The range of such beliefs derived from the qualitative study informed the design of the quantitative survey.

The quantitative study identified the following significant predictors of considered interest[1] in genetic testing for risk of major depressive disorder: self-reported history of mental illness; a higher than average self-estimation of increased risk for major depressive disorder; endorsement of the benefits of having such a test; and belief that a genetic explanation for mental illness would increase social stigma linked with these disorders. Most frequent perceived benefit was greater preparedness for accessing early psychological help, while potential for discrimination by insurance companies or employers was confirmed as the most frequently identified disadvantage of genetic testing for susceptibility to depression.

Implications of the findings for the future of psychiatric genetics and preventive interventions

The findings suggest that the use of genetic information to provide advice about risk for future depression or genetic susceptibility testing in psychiatry is likely to be well received within the community. If robustly replicated, identification of susceptibility alleles for risk of major depressive disorder are likely to lead to proposals to screen persons at increased genetic risk and provide interventions. It has been proposed that potential benefits are increased and risks are reduced when testing is limited to high risk groups when compared to screening of the general population.[1] The results confirm that population groups most likely to be amenable to genetic screening and preventive interventions in psychiatry are those who perceive themselves to have an increased risk due to family history and those who have had previous depressive episodes. This confirms the value of targeting high-risk groups for such interventions both in terms of cost-effective use of resources and identifying the population groups most likely to be receptive and find benefit. By comparison, screening the broader general population for genetic susceptibility to mood disorders is unlikely to be a practical option. While population-based screening of healthy people using a genetic test for risk of major depressive disorder, if it was available, appears to meet public acceptability; based on today's scientific evidence, such screening does not meet the criteria of high specificity, high sensitivity, high positive predictive value, high negative predictive value,

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[1] Considered interest: interest in genetic testing for depression risk once benefits and disadvantages of such testing had been explained and considered.

scientific validity or clinical utility required by population screening frameworks. Furthermore, such an approach would not be cost effective due to an unacceptable number of false positives and false negatives that would likely arise.

Interest in genetic testing to enable awareness of one's own risk for major depressive disorder and obtaining further information from a health professional suggest that there is a need for educational materials about psychiatric genetics. Such material should be tailored to individuals with an increased risk for major depressive disorder and designed to inform without encouraging unrealistic beliefs about the magnitude of risk. The findings also highlight the need for training materials on psychiatric genetics for general practitioners, psychiatrists, clinical geneticists and genetic counsellors, whom individuals interested in genetic testing will consult for further information. The existence of fatalistic and deterministic beliefs about the role of genes in major depressive disorders could deter high-risk individuals from accessing psychiatric genetic services and molecular-based preventive mental health interventions. This finding confirms that patient education initiatives about psychiatric genetics should include clear explanations about heritability, absolute risk estimates, penetrance of risk alleles and the role of environmental risk factors.

Potential differences in attitudes towards genetic susceptibility testing and risk assessment between affected[2] and unaffected individuals should be noted in future psychiatric genetic services. Despite reporting no family history of psychiatric disorders, unaffected individuals could fall into high-risk groups due to unknown family history or high environmental risk factors. Beliefs of low or no personal risk among unaffected individuals and greater hesitance about genetic susceptibility testing could preclude individuals who might benefit from early intervention from obtaining help. These factors should be considered when planning molecular-based preventive mental health interventions and public education about genetic testing for susceptibility to a psychiatric disorder.

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[2] Affected individuals were considered to be individuals reporting a personal or family history of a mental illness.

Strong interest in genetic susceptibility testing found in the quantitative study confirms the qualitative findings, but it is likely that intention to have such a genetic test may not be a true indication of uptake of a genetic susceptibility test for a multifactorial disorder, since hypothetical interest has been shown to be poor predictor of actual intention to test.[2,3] Furthermore, predictors of interest in having a genetic test for risk of depression may differ in a clinical setting. Face-to-face interaction with a genetic counsellor and/or clinical geneticist and informed pre-test consideration of the potential harms and benefits of taking a genetic susceptibility test is likely to influence uptake rates. Receiving an actual genetic result that could have a significant impact on the recipient's lifestyle, identity and biological relatives is likely to be more confronting than consideration of hypothetical risk. Uptake rates are also likely to be influenced by differences in patient perceptions about the predictive power of the genetic test in question; perceptions about potential benefits of such a genetic test, such as accessing early help; perceptions about risk for employment and insurance discrimination; and perceptions about implications for biological relatives. Variation in perception of psychosocial implications should be taken into account when planning education materials and molecular-based preventive mental health interventions.

Despite the potential for genetic discrimination to modify interest in genetic testing in psychiatry, as shown by the qualitative study, the finding of a positive significant association between perceived benefits of genetic testing for susceptibility to depression and interest in having such a test in the quantitative study suggests future users of psychiatric genetic services may believe that perceived benefits of testing may outweigh risks.[4] Nevertheless, potential for genetic discrimination in insurance and employment was rated highly as a perceived disadvantage of genetic susceptibility testing. The US Genetic Non-discrimination Act has set a precedent for international moves to put in place legislation to protect the individuals accessing future psychiatric genetic testing services from genetic discrimination, especially if molecular-based preventive mental health interventions are to be effective.

It should be noted that 'considered interest' under research conditions in which participants weighed up prescribed risks and benefits of hypothetical genetic

susceptibility testing for risk of major depressive disorder in an uncontrolled setting cannot necessarily be generalised to informed interest arising from genetic counselling in a clinical setting. In a genetics clinic, informed decisions about whether to have such a test are made following comprehensive genetic counselling involving a genetic counsellor and/or clinical geneticist. Under these circumstances, patients have the opportunity to consider the impact and possible effects of the genetic test on themselves and their family in a supportive atmosphere. The patient has a chance to fully understand the disorder associated with the genetic test and its impact, to assist with some of the issues that may arise from being identified with a genetic risk for that disorder. Thus, interest in and decisions made about genetic testing for risk of a major depressive disorder in the clinical setting may vary from the results of the present study.

It is important to bear in mind that genetic testing has the potential to detract from the detection and reduction of other potentially important environmental risk factors for major depressive disorder, highlighting the importance of providing information about contribution of non-genetic components of risk. Furthermore, given the relatively low risk rates for close family members for developing psychiatric disorders with incomplete penetrance compared to Mendelian inherited traits, risks should be kept in perspective when informing individuals of their risk and designing preventive mental health interventions. The findings from the large population survey will inform the evaluation of public interest in genetic susceptibility testing in a clinical setting and make an important contribution to public debate, public education programs and policymaking.

8.4.2 What are community preferences for the mode of access of genetic susceptibility testing?

The proliferation of commercial start-up genetic testing companies marketing genetic susceptibility tests directly to the public has raised concerns about potential health and psychosocial impact of such tests.[5] In addition to the development of genetic tests purported to predict risk for psychiatric disorders, pharmacogenomic tests have been developed that claim to predict individual response to medication,

such as suicidality in response to anti-depressants. Since recent advances in genome-wide association studies, biotechnology companies such as Navigenics, 23andMe and Knome (www.knome.com) have added 'whole genome scans' to their portfolio.

The qualitative study revealed a unanimous preference for obtaining genetic testing for depression risk through one's own doctor. Opposition to DTC genetic testing for risk of major depressive disorder was based on distrust of the credibility of DTC genetic testing services, especially if obtained via the Internet; worry about the security of their DNA sample and privacy of genetic risk information; and lack of confidence in non face-to-face genetic counselling. The quantitative study also showed that interest in accessing genetic testing for depression risk was significantly greater through one's own doctor compared to DTC from biotechnology companies after considering benefits and disadvantages of genetic susceptibility testing. Nevertheless, considered interest in accessing such a test DTC prevailed. This finding supports results of our qualitative study, which demonstrated that participants had greater trust in obtaining such a test through the medical system, with interest modified by concerns about genetic discrimination and loss of privacy.

Implications of the findings for the future of psychiatric genetics and preventive interventions

Unanimous opposition to DTC genetic testing for depression risk allele shown by the qualitative study and significantly lower interest in using DTC genetic testing services than medical services shown by the quantitative study suggest there is a low potential for the uptake of commercial genetic testing among Australian consumers. The international demand for DTC genetic susceptibility testing services is not known and such data is required before determining whether level of interest in DTC genetic testing for risk of major depressive disorder shown by the quantitative study is typical. The finding of a belief that depression-risk genotyping could be a useful part of a general health check-up suggests there could be a role for genetic risk assessment in general practice. Trust in the mainstream health system as a potential provider of genetic susceptibility testing and counselling for major depressive disorder suggests there could be an unreasonable demand on general practitioners and psychiatrists for referrals for psychiatric genetic testing.

Since interest in DTC depression risk genotyping was retained if protection from discrimination and DNA misuse could be guaranteed, current and future genetic non-discrimination legislation is likely to have a positive impact on demand for DTC genetic susceptibility testing. This will place demands on general practitioners, psychiatrists, clinical geneticists and genetic counsellors to interpret the results of psychiatric DTC genetic tests from international laboratories that they have not ordered and are not trained to interpret. Austin et al.[6] anticipated that the availability of DTC testing for psychotic disorders would justify making psychiatric genetic counselling routinely available. However, health professionals report insufficient knowledge about, and low confidence in, using genetic risk information (e.g.[7-9]), which indicates an unmet need for training materials for health professionals on psychiatric genetics, genetic test interpretation and clinical utility of the result.

8.4.3 What is the impact of a genetic model for mental illness on beliefs about stigma associated with these disorders?

Evidence of a genetic component in mental illness has the potential to reduce blame and social stigma experienced by individuals living with mental disorder (attribution theory) [10,11] and facilitate uptake of future psychiatric genetic services. Conversely genetic essentialism[12] could cause greater stigmatisation of those at risk of mental disorders, which has potential to deter individuals from accessing mental health services. Previous research on this issue has found little support for the predictions of genetic attribution theory, [13-15] which suggests progression of knowledge about psychiatric genetics could increase stigma towards individuals with, or at risk for, psychiatric disorders. This could reduce the efficacy of molecular-based preventive mental health services by modifying potential uptake of such services and causing distress to individuals obtaining genetic risk information.

The qualitative study identified contradictory beliefs that evidence of a genetic component for depression had the potential to both reduce social stigma by validating depression and other mental illnesses as physical illnesses and also increase social stigma. When this issue was tested quantitatively, a significant majority believed evidence of a genetic component for major depressive disorder

would increase stigma. There was a significant positive association between the belief that social stigma would increase and considered interest in having genetic testing for susceptibility to depression.

Implications of the findings for the future of psychiatric genetics and preventive interventions

The quantitative study is one of few to investigate the public's view on this issue. The results support previous findings that endorsement of a genetic model for major depressive disorder will increase stigma.[11, 13, 14] The finding that interest in having genetic testing for susceptibility to depression was significantly and positively associated with beliefs that evidence of a genetic component would increase rather than decrease social stigma appeared contradictory. It suggests that rather than discourage individuals from having genetic susceptibility testing in psychiatry, social stigma may not impact on choices to have genetic testing among members of the public. It could also be that favourable public views about the use genetic information as a preventive intervention outweighs concern about social stigma. The influence of stigma on individuals from families with major depressive disorder and bipolar disorder may be very different. For example, stigma by association has been identified among individuals from families with multiple relatives affected by bipolar disorder.[13]

Before interventions based on genetic risk information are implemented, education programs are needed for people at risk for a major depressive disorder to ameliorate perceived social stigma related to genetic risk information. Such programs should take into account perceived stigma by association. Patient education materials must be designed to help educate target groups about the nature of a depressive illness, its genetic and environmental components and the meaning of risk in the context of family history. The findings of the present study also suggest that there is scope for education programs for the public if social stigma arising from a genetic model for psychiatric disorders is to be addressed across society. Such measures will be needed to facilitate introduction of genetic services in psychiatry and success of such services.

8.4.4 Are healthy individuals prepared to modify risk for depression at a pre-symptomatic stage through preventive behaviours?

Genetic testing in psychiatry may provide information that can lead to behaviours that promote health and reduce risk for disease. Current knowledge about health behaviours as a result of genetic testing comes predominantly from studies involving Huntington disease and breast and ovarian cancer.[3, 16] According to theories of behavioural change described in Chapter 6 and several empirical studies,[17-19] it is likely that causes attributed to mental illness influence perceptions about what kind of interventions might be effective in reducing risk or preventing disease. Studies of risk reduction behaviours among healthy adults following genetic susceptibility testing for multifactorial adolescent and adult-onset diseases are required to inform the planning and monitoring of health promotion and risk-reduction strategies associated with genetic testing for present and future use.

Qualitative analysis revealed that anticipated risk-reducing behaviours in response to hypothetical genetic testing for risk of major depressive disorder included vigilance for signs and symptoms of depression for self and family and seeking medical information. Anticipated lifestyle changes included modification of stress, diet, exercise and drug and alcohol intake. Mixed beliefs prevailed about whether stress could be modified or avoided. Perceptions arose that individual differences in response to stress would impact on the efficacy of preventive strategies. Hypothetical genetic risk information also prompted anticipated preventive behaviour such as the learning of coping strategies in advance to minimise the risk of or prevent depression and starting a course of anti-depressants.

The quantitative study found strong community receptiveness to behavioural preventive mental health interventions in association with genetic testing for risk of depression. The most highly ranked anticipated preventive behaviours in response to hypothetical depression risk genotyping was 'helping children be resilient to stress' followed by 'intention to modify potential life stressors,' 'intention to start therapies' and 'reduce excessive drug use.' The study found hypothetical depression risk genotyping had little impact on anticipated reproductive decisions. Target groups most likely to engage in such interventions were those with a high self-

reported risk of major depressive disorder and those who endorse the view that mental illness may develop from both genetic and modifiable environmental risk factors.

Implications of the findings for the future of psychiatric genetics and preventive interventions

Benefits from genetic susceptibility tests can only be realised if major depressive disorder or some of its consequences can be prevented or ameliorated, for example by allowing those at higher risk to make better informed life choices. The findings suggest the public would be receptive to preventive interventions designed to reduce risk of a major depressive disorder.[20] Greater preparedness for accessing early psychological help and minimising stress are consistent with previously reported beliefs that genetic risk information could facilitate prevention and earlier intervention of major depressive disorder.[21] This indicates that rather than waiting for people to become unwell enough to seek help, prevalence of depression could be reduced by making preventive education about depression available to the public and risk groups at a presymptomatic stage. Individual skill-learning approaches could be adapted from cognitive behavioural therapy methods, using the mass media to disseminate the intervention, as demonstrated by the San Francisco Mood Survey Project discussed in Chapter 2.5.[22] This strategy could be particularly valuable if high-risk subgroups could be identified and targeted within at-risk populations.

Those charged with designing molecular-based preventive mental health interventions for psychiatric disorders should consider potential communication issues between clinician and patient since individual interpretation of the predictive power of genetic variants associated with depression may be variable. This may especially be the case for patient and public understanding of risk probabilities.[23] The issue of false-positive results should be given particular attention since 'good' or 'bad' results have considerable potential to radically alter self-perception, individual life choices, and the risk of social stigma as discussed in Chapter 8.4.3. It is important that these issues are studied before genetic susceptibility testing or the use of genetic risk information becomes standard clinical practice in psychiatry. Anticipated obstacles to the efficacy of such interventions include the possibility that fatalistic interpretation of a predisposition to depression may lead to unhealthy

behaviours or preventive inaction. Furthermore, despite growing evidence that depressive symptoms can be reduced, the literature is inconclusive as to whether depressive episodes or high levels of depressive symptoms can be prevented.[24] It is important that empirical studies using educational interventions are developed to replace current assumptions, speculation and conjecture about anticipated behavioural response to genetic risks.

8.4.5   How do the media portray psychiatric genetics and genetic testing?

The media are highly influential as an agenda setter (shaping public thinking) and agenda builder (influencing policy).[25,26] Thus the way psychiatric genetics is portrayed in the media has ramifications for clinical psychiatry and uptake of genetic technology. Chapter 7 explored how Australian print media depicted the relationship between mental illness and genetics across 14 years. The aim of the study was to identify which aspects of psychiatric genetics have received greatest attention in the media in recent years and analyse media framing of such topics. This provides an opportunity to systematically examine the likely influence of the mass media on public attitudes towards psychiatric genetics and development of policy.[27]

The media analysis found that coverage of psychiatric genetics in the Australian print news media has steadily increased since 1996. Items attributing the aetiology of psychiatric disorders to gene-environment interactions predominated. However, of items which referred to heritability of mental illness, the frequency of reports using deterministic framing was significantly greater than that of reports that used probabilistic framing. Media predictions about the future of psychiatric genetics included further discovery of genetic markers associated with psychiatric disease; discovery of genetic markers linked to response to psychotropic medication (pharmacogenetics); genetic tests that will predict risk of psychiatric disorders; and future availability of molecular-based interventions for mental illness. Of the clinical benefits predicted to occur by the end of 2009, the majority failed to manifest. Psychosocial implications of psychiatric genetics received comparatively little coverage.

Implications of the findings for the future of psychiatric genetics and preventive interventions

How the outcome of psychiatric genetic research is framed in the media has the potential to influence: public attitudes to mental illness and its causes; interest in, and uptake of, new technologies in psychiatry, such as genetic testing; and engagement in preventive interventions. The media analysis suggests that the public endorse genetic research in psychiatry and potential mental health benefits, which could stimulate a high interest in psychiatric genetic testing if it becomes available.[28]

While the media examined in the present study appear to predominantly frame psychiatric disorders as developing from both genetic and environmental risk factors, over emphasis of the predictive power of a genetic component suggests individuals seeking future preventive interventions may favour biological rather than environmental strategies to modify risk. This could pose a challenge to the success of preventive interventions, which will depend on public understanding of the interactive effect of genotype and environmental risk factors. Deterministic headlines and frequent portrayal of psychiatric genotypes as having definitive risk could distort public understanding of the influence of genes in multifactorial disease and perpetuate beliefs that genetic information alone provides definitive solutions, which could impact on future options for preventing, treating and managing mental illness.

Disproportionate optimistic coverage of perceived clinical interventions resulting from psychiatric genetic research, such as customised genetic tests and treatment, compared to critical commentaries about ethical and psychosocial implications, could result in unrealistic public expectations of how genetic risk information might resolve mental health problems, with insufficient awareness of the limitations of genetic testing. Low media profile of these issues indicates the public may not be well informed about the implications of obtaining a genetic test for a psychiatric disorder that provides only probabilistic risk and the potential for insurance discrimination based on a disorder that may never develop. Low media profile of privacy issues suggests that individuals purchasing DTC genetic tests may not be fully aware of the complexities of informed versus presumed consent as outlined in Chapter 2.6.3. It also suggests the public purchasing such tests may be unaware that

personal genetic information could be later resold and used in commercial research. Media treatment of genetic information for psychiatric disorders as a commodity could encourage these practices.

Marginalising of stigma issues, the right to know or to not know one's genetic risk, impact on relatives, and the potential for eugenics suggests that these psychosocial implications are low on the public and political agenda. It will be necessary to raise the profile of psychosocial and ethical implications surrounding the use of genetic information to ensure that these issues keep pace with the rapid advances in genetic research.

Solutions can be found by harnessing the media's role as an agenda setter and agenda builder. The research community has an opportunity to influence the mass media's selection of topics to shape the debate on psychosocial and ethical issues surrounding the use of genetic information in psychiatry, and thus change the social and political environment in which decisions about health and health resources are based. The media can also be used as an effective catalyst for strategic communications to inform and influence individual and community decisions that enhance preventive behaviours and mental health.

8.5   General strengths and limitations of the methodology

A number of methodological limitations were discussed in each of the empirical studies. The three studies benefited from rigorous scientific methods, which increase their ability to reproduce the findings. The following section is not aimed at revisiting specific limitations of each of the studies but instead aims to discuss *general* strengths and limitations of the methods employed not already covered in the relevant chapters.

One of the strengths of the qualitative study based on focus group methodology is that it provides a rich source of data on the range of attitudes towards psychiatric genetics and genetic testing. The inclusion of quotes from participants provides

graphic and easily understood information. The qualitative approach allows the potential for new insights into the topic being investigated and opening of new lines of inquiry according to the direction of the focus group discussion.[29] The structured nature of the focus group discussion guide in this thesis did not preclude evolution of the discussion into related lines of inquiry, adding richness to the data. This kind of information gives additional meaning and value to current knowledge about psychosocial implications of psychiatric genetic, which provides an appropriate basis from which to inform the design of the population survey for the quantitative stage of this thesis.

One of the shortcomings of qualitative analysis is that it cannot establish causality between different research phenomena. Furthermore, the results cannot be generalised to wider populations. Also, in qualitative studies participants may be selective about information they choose to impart; consequently a qualitative approach does not lend itself to systematic comparisons between individual or groups of informants.[29] Voluntary reporting of a personal or family history of mental illness could be a limitation of the present study since this may have resulted in the affected group only being represented by those opting to disclose such information.

The strengths of the quantitative study included its large sample size, identification of specific dependent and independent variables, the hypothesis-driven approach, and the reaching of objective conclusions. In opposition, the structured format with closed type questions limited responses to only those outlined in the original research proposal with no scope to pursue serendipitous lines of reasoning. Furthermore, variation in how a question is interpreted could confound the findings. However, the advantage of the telephone survey compared to paper- or web-based surveys is that the interviewer can prompt the respondent with prescribed information to prevent misunderstandings. Sampling and weighting bias in a quantitative study can undermine the accuracy, validity, and generalisation of the findings. In the present study, there was a participation bias towards older age groups and females, which is common in public health surveys.[30,31] The study used strategies known to minimise self-selection bias caused by non-response, including randomisation of participant selection per household, achieving a moderately high

response rate, and controlling the results for demographic confounders.[22, 32] Future surveys of this nature should be designed to include users of mobile phones to ensure normal distribution of age and sex. Furthermore, data collected in this study could be weighted by age and sex to increase ability to generalise the findings.

The media analysis presented in this thesis used qualitative content and framing analysis, which are preferred methods for qualitative assessment of the prevalence of specific types of content in the media and how they are presented.[33] The method involves the use of systematic procedures to enable inference of media content, drawing on representative samples of content to describe social phenomena. Its strengths lie in its reliance on the scientific method to categorise all forms of content, such as the use of intercoder reliability measures. The media analysis conducted as part of this thesis conformed to content analysis rigour and was highly systematic and achieved good reliability (agreement between independent coders). How reliability should be measured is a source of contention among media theorists, as described in Chapter 7.

Limitations of qualitative content and framing analysis are similar to those pertaining to other qualitative methods that rely on coding, since coding by different coders can be inconsistent and lead to discrepancies. Without acceptable measures of reliability, content analysis has its limitations. This problem can be overcome to some extent by adherence to rigorous inter-coding methods. However, the self-limiting nature of coding schemes developed *a priori* may inhibit innovation and exploration of ideas. To enable full extraction of codes much of the exploratory work can be done before the coding scheme is finalised.[34]

While content analysis is a powerful way to examine what messages people are exposed to in the media, the method does not translate to an understanding of how effective these messages might be in changing health behaviour. Also, there are no guidelines on how to evaluate the results, thus the analysis is vulnerable to subjective interpretation. The results of the present media analysis will inform further research on how the portrayal of psychiatric genetics might impact on its audience. Generalisability to other media types of print media published in other countries is limited.

8.6   Recommendations for future research

There is a dearth of professional guidelines to assist in the transition towards genetic susceptibility tests and the use of genetic risk information about mood disorders based on family history from research into clinical practice.[35] Education strategies for users of genetic risk information and training materials for health professionals charged with their care will be required to ensure appropriate application of genetic testing in health care delivery, including preventive health. Thus a research agenda is proposed in which various avenues of investigation are identified that would aid future understanding of the responsible use of genetic information in clinical practice and development of molecular-based preventive health interventions in psychiatry.

8.6.1   Training

The first component of such an agenda relates to the need to develop and rigorously evaluate innovative training interventions for health professions working in clinical genetics and psychiatry with evidence-rated information on managing patients with a hereditary risk for psychiatric disorders and the provision of advice on evidence-based and recommended preventive strategies.

Rapid advances in psychiatric genetic research means health professionals, including psychiatrists, clinical geneticists and genetic counsellors, will be increasingly called upon to incorporate genetic risk and family history information about conditions such as major depressive disorder and bipolar disorder into clinical practice. One study has shown that the majority of participants reported being interested in obtaining such information directly from health professionals (in particular, experts in depression).[36] Studies demonstrate positive attitudes towards genetic testing for susceptibility genes associated with major depressive disorder and bipolar disorder among the public, patients and relatives (e.g.[4, 36-39]), but little is known about the attitudes of the health professionals who will manage such patients.

Health professionals will need to be knowledgeable about the genetic contribution to psychiatric disorders, recurrence risk estimation, decision-making about options for dealing with recurrence risks, and how genetic risk information might be used to help patients make reproductive decisions or engage in preventive health behaviours.[40] No systematic data are currently available on Australian health professionals' attitudes, beliefs and level of knowledge about psychiatric genetics. No quality evidence-based training materials exist internationally which are targeted at psychiatrists, clinical geneticists and genetic counsellors about the modern application of psychiatric genetic medicine, such as genetic susceptibility testing.

Despite the potential value of information provision about genetic risk, a US survey of genetic counsellors showed that counsellors feel ill equipped to raise the issue of psychiatric disease with clients.[9] Similarly, another US survey shows that psychiatrists are unfamiliar with many relevant aspects of medical and psychiatric genetics.[8] Anecdotal evidence suggests that Australian health professionals feel similarly unprepared to provide patients with genetic risk information. Factors contributing to professionals' reluctance to provide expert advice about genetic risk may include the lack of training in psychiatric genetics, lack of patient education materials as well as the absence of counselling tools to supplement expert counselling. Importantly, anecdotal evidence also suggests that many health professionals experience the provision of empiric and individualised recurrence risk as extremely challenging, given the wide variation of recurrence risks reported in the literature, the lack of data on empiric risk available on more complex family relationships (e.g. risk associated with having a 2nd degree rather than 1st degree relative with depression, presence of multiple affected relatives on either one side only or both sides of the family), and the possible presence of a heterogeneous group of disorders within a given family.

8.6.2 Interventions

The second component of an agenda for further research relates to the need to develop and rigorously evaluate an educational intervention for individuals with a family history of mood disorders. It is recommended such information should

include education about the genetic contribution to such disorders, recurrence risk estimation and facilitation of decision-making about options for dealing with recurrence risks and whether or not to have children.[40]

An emerging body of literature is available that demonstrates that people with a family history of depression may benefit from genetic risk information or decision support interventions related to their increased genetic risk and increased risks to their offspring. Professional guidelines suggest that genetic risk information should be offered to people with bipolar disorder and their families, particularly those who are considering having children.[41] Studies of individuals and families with bipolar disorder suggest that patients and families overestimate recurrence risks in first degree relatives.[42] Information on genetic risk for depression for at-risk individuals should be accompanied by the provision of advice on early detection, risk management and prevention. For example, at-risk individuals should be advised to undergo regular screening by a health care provider, such that appropriate interventions can be provided in a timely manner, thus improving prognosis.

8.6.3   Can depression be prevented?

While several of the risk factors for major depressive disorder cannot be changed (e.g. family history), at-risk individuals are likely to benefit from accurate and up-to-date information on risk factors that are amenable to change (e.g. substance abuse), and/or strategies they may adopt to reduce their risk (e.g. getting adequate exercise and/or sleep).

Risk management strategies may be either evidence-based (e.g. cognitive behavioural therapy, regular exercise) or represent potential risk-reducing strategies that correspond to universally recognised standards for healthy living (e.g. avoiding illicit drugs and excessive consumption of alcohol, or getting adequate sleep). Evidence is available from randomised control trials and meta-analyses that cognitive behavioural therapy and other types of psychological interventions may prevent depression in children, adolescents and adults.[43-45] A recent meta-analysis shows that depression prevention programs involving psychological interventions in

general and at-risk populations of children and adolescents lead to short-term reductions in depressive symptoms and diagnoses of depressive illness.[43] For example, using a randomised control trial design, group cognitive behavioural therapy has been shown to be superior to usual care for the prevention of depression in adolescent offspring of parents with a history of depression.[44] Randomised control trials that assessed the efficacy of psychological treatments in adults in the prevention of the first onset or relapse/recurrence of depressive disorders are also available.[45] These randomised control trials show that interventions such as cognitive behavioural therapy are effective in reducing the incidence of depression by about 50%, and that interventions targeting specific high-risk populations are even more effective.[45]

8.6.4 What population groups should be targeted?

Since first onset for psychiatric disorders typically occurs in adolescence or early adult life,[46] early identification is important to prevent or minimise long-term adverse effects and to use this understanding for optimising interventions. A pilot study of 31 individuals with bipolar disorder has confirmed very high interest in genetic counselling.[42] Austin et al.[47] suggest that adult children, siblings and parents of affected individuals; affected individuals and their partners planning their families; and affected people who maintain high-risk behaviours may all benefit from genetic counselling in particular.

8.6.5 Key future considerations

Future research should focus on answering further questions pertinent in this area. It will be necessary to determine the clinical utility of identifying people at increased risk for major depressive disorder on the basis of family history and/or genetic risk variants; the effectiveness of educational interventions about genetic and environmental risk for mood disorders, targeting of high risk groups; the effectiveness of training programs about psychiatric genetics targeting psychiatrists, geneticists and genetic counsellors; the population groups which gain optimum benefit and should be targeted for genetic-based preventive interventions in

psychiatry; how target groups should be approached; how molecular-based preventive interventions in psychiatry should be disseminated; how molecular-based preventive programs in psychiatry could be disseminated most effectively and efficiently; and the optimal timing of depression prevention strategies.

8.7 Conclusions

The research carried out for this thesis has allowed examination of some key areas that continue to preoccupy investigation into psychosocial aspects of psychiatric genetics. The findings contribute research evidence to global imperatives highlighted by the WHO, the Department of Health in the UK and the Commonwealth Department of Health and Ageing in Australia to identify potentially effective psychosocial interventions and prevention strategies as outlined in Chapter 1. In particular, it provides an empirical investigation of the perceived impact of a genetic model for major depressive disorder on public and patient engagement in psychiatric genetic services and associated mental health interventions. These findings will assist global consultation about the complexities that should be considered by those charged with the development of a register of genetic tests, policies to regulate DTC genetic susceptibility testing, and legislation to protect individuals who access genetic susceptibility tests. Further research is needed to develop interventions such as educational materials for high risk groups and psychiatric genetic training materials for health professionals before molecular or hereditary-based preventive interventions can be implemented to reduce the burden of suffering from major depressive disorder and other psychiatric disorders.

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Appendix A – Study Materials for Qualitative Study (1A, 1B)

A.1   **Focus Group Discussion Schedule**

A.2   **Demographic Survey**

A.3   **Participant Information Statement**

A.4   **Participant Consent Form**

A.1 – FOCUS GROUP DISCUSSION SCHEDULE

`PSYCHOSOCIAL IMPACT OF PSYCHIATRIC GENETICS´

Introductory statement by facilitator

- Hello, thank you for agreeing to take part in this discussion group about genetics and psychiatric disorders. My name is Alex Wilde from the University of New South Wales and this is Dr Bettina Meiser, who is Head of the Psychosocial Research Group at the Prince of Wales Hospital at Randwick. The discussion today is about the impact of genetic information about psychiatric disorders, specifically depression, bipolar disorder and schizophrenia.
- Please read the information sheet in front of you and sign the consent form.
- Please also complete the short demographic survey & put on your name tags.
- Purpose of the present study
  - Through this study we hope to learn more about what people understand about the role of genes in depression, bipolar disorder and schizophrenia; find out more about peoples' attitudes towards advances in research into genetics of psychiatric disorders, such as genetic testing, and perceived personal and social implications of genetic information about these disorders.
  - Part of the study includes finding out how people understand and interpret information about genes and psychiatric disorders read in the media and how media reports influence perceived implications of genetic information about depression, bipolar disorder and schizophrenia.
- Reasons for digital recording of session.
  - The discussion today will be digitally recorded in order to obtain an accurate transcript of everything that is said. The recording device is there (points) and is now switched on. Participant identifying details will not be recorded and will remain confidential. The digital recordings will only be accessible by researchers immediately involved in this study and any resulting publications of the study results will not contain any identifying details of the participants.

- Role of facilitators
    - The two facilitators here today, Bettina and myself are here to help structure and guide the discussion which is designed around some questions related to genetics and psychiatric disorders. Bettina's role will predominantly be as a scribe and I will be the main facilitator.
- Ground rules for focus group
    - Interested in hearing from everybody
    - No right or wrong answer- want to hear your views
    - One person at a time
    - Confidentiality
    - Respect for other views/ speak for oneself.
    - Keep to discussion focused on depression, bipolar disorder and schizophrenia as psychiatric disorders in question.

Could you please start off by introducing yourself (by first name only) and briefly telling the group very briefly your interest in this discussion topic.

Part I. Psychosocial impact of psychiatric genetics and genetic risk information

In this part I would like you to discuss your views on the contribution of genetics to psychiatric disorders*, in particular: what you understand about the role of genes in the development of depression, bipolar and schizophrenia and your views on any social implications arising from genetic information linked to psychiatric disorders.

*"Psychiatric disorders" refers to depression or bipolar disorder or schizophrenia or all three. In your responses please specify depression, bipolar disorder or schizophrenia if and where necessary.

1) What are the possible cause(s) of depression, bipolar disorder or schizophrenia? (Referred to collectively from now on as 'psychiatric disorders'* but specify which disorder you are talking about where appropriate).

2) What do you understand about the inheritance of genes that might influence the development of a psychiatric disorder?
   (Prompts)
   a. *Do genes cause psychiatric disorders*?*
   b. *Do genes confer increased risk – ie a susceptibility (explain: vulnerability or predisposition) to mental illness in interaction with other factors?*
   c. *Can have a certain risk gene or genes but not develop disorder (incomplete penetrance)?*
   d. *Is there no genetic basis for these disorders?*

3) Does genetic risk information about psychiatric disorders* have positive or negative social implications, and if so what are they?
   (Prompts)
   a. *Potentially increase stigma and discrimination (by labelling esp. pre symptomatically)?*
   b. *Help legitimise these illnesses?*
   c. *Help people take control of their mental health?*
   d. *Increase expectation of a 'cure'?*
   e. *Increase support for eugenics?*
   f. *Does it depend on the disorder in question / certainty of risk?*

4) If a genetic test for susceptibility to a psychiatric disorder*, was available would you want the test and why?

   (Prompts)

   a. *Would you be more interested in a having a test or less interested if a close family member already has a mental illness* ?*

   b. *Would you tell your family you are having a test/ your result?*

   c. *Would a-c depend on which disorder / on certainty of risk?*

   d. *What are the benefits or negative consequences of knowing your risk?*

5) If a close relative had a test and was found to be at increased genetic risk for a psychiatric disorder*, would you:

   a. Want to be tested?

   b. Have your children tested?

   (Prompts)

   c. *Depends on which disorder?*

   d. *Depends on certainty of risk?*

6) A genetic test is available via the internet that can identify a variation of the serotonin transporter gene (facilitates movement of the feel good brain chemical serotonin around the brain) that is thought to cause a vulnerability to depression. I will briefly explain. You may have one of three varieties of the serotonin transporter gene. They are: short/short; long/long; or short/long. The short or long refers to the length of the gene. People with the short/short (one short inherited from each parent) are thought to have an increased vulnerability for depression if they also encounter three or more stressful events. In other words they may be more susceptible to stress which can lead to depression. The long/long version is thought to make people predisposed to increased resilience. Short/long is somewhere in between

   The serotonin transporter genetic test is available over the internet without going to a doctor or medical centre for . Now you know there is a real test available that provides an indication of predisposition to depression - would you now want to have the test? If so why?

   (Prompts)

   a. *Depends on certainty of risk?(short/short = 80%; long/long 30%)*

   b. *What are the benefits or negative consequences of knowing your risk?*

7) If you were found to have a genetic make up that put you at increased risk of a psychiatric disorder*, how do you think it would it affect your life?

(Prompts)

    a. *Change lifestyle to reduce environmental risk factors etc?*

    b. *Change the way you view psychiatric disorders?*

    c. *Seek advice on preventive health care?*

    d. *Be concerned about privacy of your genetic information?*

    e. *Depend on which disorder?*

    f. *Depend on certainty of risk?*

A.2 - FOCUS GROUP DEMOGRAPHIC SURVEY

1. First name _____

2. Age _____

3. Sex
   a. Male   b. Female

4. Main languages spoken at home
First_____

Second language spoken at home (if applicable) _____

5. Highest education level (please circle)
   a. Tertiary degree or professional qualification
   b. Trade qualification
   c. Year 12
   d. High school

6. Occupation or other_____

7. Prior scientific or medical knowledge
   a. Specialised (professional)
   b. Well-informed lay person
   c. Average
   d. Low
   e. Nil

8. Newspapers read
Please list up to three main newspapers you read regularly. Please state NIL if you

don't read newspapers.

_____

_____

_____

9. How often do you read newspapers?
   a. Regularly
   b. Sometimes
   c. Never

10. What is your primary source of scientific or medical information?
   a. Newspapers and magazines
   b. Other media eg TV, radio, internet
   c. Popular science text books

d. Scientific and medical journals
e. Other (please state)_____

THANK YOU

A.3 – PARTICIPANT INFORMATION STATEMENT

University of New South Wales
The Prince of Wales Hospital
Barker Street Randwick
NSW 2031 Australia

SCHOOL OF PSYCHIATRY
UNIVERSITY OF NEW SOUTH WALES
BLACK DOG INSTITUTE
HOSPITAL ROAD
PRINCE OF WALES HOSPITAL,
RANDWICK, NSW, AUSTRALIA 2031

TEL: 61-2-9382 8511

FAX: 61-2-9382 8151
E-MAIL: alex.wilde@unsw.edu.au

Approval no.: 07237

THE UNIVERSITY OF NSW
PARTICIPANT INFORMATION STATEMENT
AND CONSENT FORM

Title of project: 'The psychosocial impact of psychiatric genetics'

I am contacting you today to invite you to participate in a study on public views about genetic issues concerning depression, bipolar disorder and schizophrenia. We hope to learn more about public understanding about the role of genes in depression, bipolar disorder and schizophrenia. Part of the study includes interpretation of media reports about research into genetics linked to depression, bipolar disorder and schizophrenia.

The information that will be collected as part of this study will be used with the aim of improving public understanding about mental health and genetics, reducing stigma associated with psychiatric disorders; informing future mental health care associated with genetics, and improving quality of reporting in the media on the subject of psychiatric genetics. Participants are being selected at random by Lawre Suttor Research from their database.

If you decide to participate in this study, you will be participating in a small group discussion called a focus group with other members of the public who have also been selected at random. Ms Alex Wilde, PhD candidate in psychiatry and Dr Bettina Meiser, Head of Psychosocial Research Group, Prince of Wales Hospital will be present and will guide the discussion group. The discussion will be digitally recorded and last for about two hours. There are no known risks or benefits associated with participation in this study.

Any information that is obtained in connection with this study and that can be identified with you, will remain confidential and will be disclosed only with your permission or except as required by law. If you give us your permission by signing this document, we plan to publish the results as a journal article for submission to a specialist journal to ensure that the findings will be disseminated to a wider readership. In any publication, information will be provided in such a way that you cannot be identified.

Complaints may be directed to the Ethics Secretariat, University of NSW, Sydney, NSW 2052, Australia, Tel. 9385 4234, Fax 9385 6648, e-mail: ethics.sec@unsw.edu.au.

Your decision whether or not to participate will not prejudice your future relations with the University of New South Wales or your general health care. If you decide to participate, you are free to withdraw your consent and to discontinue participation at any time without prejudice.
If you have any questions, please feel free to call us. If you have any additional questions later, Alex Wilde (Tel 9382 8511) or Dr Bettina Meiser (Tel 9382 2638). You will be given a copy of this form to keep.   Page 1 of 2

THE UNIVERSITY OF NSW

PARTICIPANT INFORMATION STATEMENT
AND CONSENT FORM (continued)

Title of project: 'The psychosocial impact of psychiatric genetics'
You are making a decision whether or not to participate. Your signature indicates that,
having read the information provided above, you have decided to participate.

_____   _____
Signature of participant   Signature of witness

_____   _____
Please PRINT name   Please PRINT name

_____   _____
Date   Nature of witness

_____
Signature of investigator

_____
Please PRINT name

REVOCATION OF CONSENT
Title of project: The psychosocial impact of psychiatric genetics

I hereby wish to **WITHDRAW** my consent to participate in the research proposal described
above and understand that such withdrawal **WILL NOT** jeopardise any treatment or my
relationship with the University of NSW.

_____   _____
Signature   Date

_____
Please PRINT name

Please forward the section for revocation of Consent to:

Alex Wilde
PhD candidate
Black Dog Institute
Hospital Road
Prince of Wales Hospital, Randwick, NSW 2031   Page 2 of 2

Appendix B – Study Materials from Quantitative Study (2A, 2B)

B.1   **CATI Survey**

B.2   **Interviewer training manual**

B.3   **Participant Information Statement**

B.4   **Participant Consent Form**

B.1- CATI SURVEY

```
!DO ID
!set color to n/w,w+/b,b+/n
------------
QID,s,0,0
-------------
!DO INTRO1
------------
QINTRO1,s,0,0
-----------
!DO INTRO2
------------
QINTRO2,s,0,0
-----------
!clear
!@ 10,0 say "DETERMINE THE RESPONDENT'S LANGUAGE(S) AND/OR COUNTRY OF
ORIGIN"
!@ 12,0 SAY "LANGUAGE(S)" GET LANG
!@ 14,0 SAY "COUNTRY" GET COO
!@ 18,0 say "Thank you for your time. "
!READ
--------------
langcob,x,0,0
--------------
IF rrate<>1 .and. rrate<>3
PHONE NO. IS ("+rtrim(std)+") "+phone+"


Good afternoon/evening, my name is _____. I'm calling about a
study
being conducted by the Faculty of Medicine at the University of New
South
Wales.


We'd like to complete a short interview with a member of your
household asking
```

about their views about mental illnesses.

[INTERVIEWER: OFFER FREECALL/LETTER/CONTACT NUMBER IF HOUSEHOLD
REFUSAL]

[IF ASKED: 'We randomly generated the telephone number we contacted
you on.

      The Faculty of Medicine at the University of New South
Wales does

      medical research, including research into mental
illness.']

\#   [1. YES - CONTINUE]

     13. REQUIRE LETTER TO CONTINUE

     21. NEGATIVE HOUSEHOLD REACTION

     22. HOUSEHOLD REFUSAL 14. LANGUAGE PROBLEM 18. WRONG
NUMBER/Area

     24. NO RESPONSIBLE ADULT AT HOME - RESPONDENT NOT KNOWN

      CALLBACK ARRANGED (FOR A TIME WITHIN THE SURVEY PERIOD)

     44. CALLBACK ARRANGED 9. BUSINESS [6. Unsuitable]

```
qnolet1,n,2,0,13,15,1,21,22,24,18,44,9,6
!do case
! case qnolet1=1
!  skipto ="QHSIZE"
! case qnolet1=14
!  do langcob
!  repl rrate with qnolet1
!  skipto="QENDBIT"
! case qnolet1=15
!  repla rrate with 15
!  skipto="QENDBIT"
! CASE qnolet1=13
!  SKIPTO="QPOST1"
! OTHERWISE
!  repl rrate with qnolet1
```

```
!  skipto="QENDBIT"
!endcase
----------------
IF rrate<>1 .and. rrate<>3
```

Firstly, can you tell me how many people aged 18 and over live in your

household?
[EXPLAIN IF NECESSARY THE RESPONDENT MUST BE CHOSEN BY COMPUTER]


```
#     [NUMBER OF PEOPLES AGED 18 AND OVER - 9.=9 or more ELIGIBLE]
      15. NO ELIGIBLE PERSON
      13. REQUIRE LETTER TO CONTINUE

      23. IF THERE IS ONE ELIGIBLE PERSON WHO IS NOT THE SPEAKER
      99. REFUSED QUESTION BUT WISHES TO CONTINUE - AND H/H ELIGIBLE



      [IF ABSOLUTELY REFUSES TERMINATE AND Pg Up]

---------------------
qhsize,n,2,0,1,9,99,23,15,13
!do case
!case qhsize=13
! skipto="QPOST1"
!case qhsize=15
! skipto="QENDBIT"
! replace rrate with qhsize
!case qhsize=23
! skipto="QPERSHOM"
!case qhsize=99
! skipto="QPERS"
!endcase
!if qhsize=1.or.qhsize=23
! replace ragepos with 1
!ENDIF
```

```
-------------------
IF rrate<>1 .and. rrate<>3


!if qhsize=1
Are you aged 18 or over [EMPHASISE AGE RANGE]
!else
! if qhsize=2
Are you the older or the younger of the people aged 18 or over?
! else
Are you the oldest, the 2nd oldest, 3rd oldest, etc.
of the people aged 18 or over?
! endif
!endif


#     "+iif(qhsize=1,"[1. YES - PERSON AGED 18 OR
OVER]",iif(qhsize=2,"[1. OLDER  2. YOUNGER]","[1. OLDEST  2. 2ND
OLDEST  3. 3RD OLDEST ... ETC.]"))+"
    77. SPEAKER OUTSIDE AGE RANGE - SPEAKER NOT ELIGIBLE]
    99. REFUSED TO ANSWER (BUT WILL CONTINUE)


-------------------
qsposit,n,2,0,1,9,77,99
!do case
!case qsposit=1
! if qhsize=1
!*  if qremlet1<>19.and.letter=1
!*   skipto="QREMLET2"
!*  else
!   skipto="qsend"
!*  endif
! endif
!case qsposit=77
! if qhsize=1
!   skipto="QPERSHOM"
! else
!  skipto=skipto
!endif
```

```
!case qsposit=99
  skipto=skipto
!endcase
-------------------
IF rrate<>1 .and. rrate<>3
!xpers=mod(int(random(id)*100000),qhsize)+1
!do case
! case xpers=1
!   xpext=""
! case xpers=2
!   xpext="second "
! case xpers=3
!   xpext="third "
! case xpers>3
!   xpext=str(xpers,1)+"th "
!endcase
!if qhsize<>0
! if qhsize=1.or.qhsize=23
!   replace ragepos with 1
! else
!   replace ragepos with xpers
! endif
!endif
!if qhsize<>23.and.qhsize<>1.and.qhsize<>99.AND.QSPOSIT<>99
The computer has chosen
"+iif(xpers=qsposit,"you",iif(qhsize=2.and.xpers=2,"the younger
person","the "+xpext+"oldest person"))+"
as the one I should speak to from your household.
!endif
!if qhsize=99.OR.QSPOSIT=99
The computer has chosen the person in your household with the LAST
birthday
as the person I should speak to. [REPEAT AGE RANGE IF NECESSARY]
!endif

!if qhsize=1.or.qhsize=99.OR.QSPOSIT=99
Would that be yourself?
```

```
!endif


[INTERVIEWER: FREECALL/LETTER IF HOUSEHOLD REFUSAL]


     [13. REQUIRE LETTER TO CONTINUE]
#   "+iif(qhsize<>1.and.qhsize<>99.AND.QSPOSIT<>99,"<Enter> to
continue","")+"
    "+iif(qhsize=1.or.qhsize=99.OR.QSPOSIT=99," 1. Yes  2. No
","")+"22. HOUSEHOLD REFUSAL  14. LANGUAGE PROBLEM
    66. PERSON UNAVAILABLE FOR REST OF SURVEY PERIOD - EXPLAIN IN
COMMENTS
    6. PERSON UNSUITABLE - EXPLAIN IN COMMENTS
!if id>999999
#
!endif
---------------------
qpers,n,2,0,0,2,22,66,14,6,13
ragepos,n,2,0
!if .not. ck()
!do case
! case qpers=1
!  skipto="qsend"
! CASE QPERS=2.or.qpers=0
!  if ragepos=qsposit
!   skipto="qsend"
!  else
!   SKIPTO=SKIPTO
!  endif
! case qpers=13
!  repl rrate with qpers
!  skipto="QPOST1"
! case qpers=14
!  do langcob
!  repl rrate with qpers
!  skipto="QENDBIT"
! OTHERWISE
!  repl rrate with QPERS
```

```
!*  if letter=1.and.qpers=22
!*   skipto="QREMLET2"
!*  else
!   skipto="QENDBIT"
!*  endif
!endcase
!endif
----------------------
IF rrate<>1 .and. rrate<>3 .and.
(qpers=2.or.qpers=0.or.qpers=9.or.qhsize=23)
!if qpers=9
Good afternoon/evening, my name is _____. I'm calling on behalf
of the
Faculty of Medicine at the University of New South Wales.

Could I please speak to ..... [CHOSEN RESPONDENT].
!else
Could I please speak to that person.
"+iif(qhsize<>23.and.qhsize<>1.and.qhsize<>99,"[ie SELECTED OTHER
PERSON IN HOUSEHOLD]","")+"
!endif

WAIT TILL CERTAIN OF ACTUAL RESPONSE BEFORE PROCEEDING

[INTERVIEWER: OFFER FREECALL/LETTER IF HOUSEHOLD REFUSAL]

#   1. YES  2. NO - NOT AVAILABLE    22. No [HOUSEHOLD REFUSAL]
   [13. REQUIRE LETTER TO CONTINUE]
    14. LANGUAGE PROBLEM
    66. PERSON UNAVAILABLE FOR REST OF SURVEY PERIOD
     6. PERSON UNSUITABLE - EXPLAIN IN COMMENTS
-----------------------------
qpershom,n,2,0,1,2,14,66,22,6,13
!do case
! case qpershom=66
!  repl rrate with 66
!  skipto="QENDBIT"
```

```
! case qpershom=6
!  repl rrate with 6
!  skipto="QENDBIT"
! case qpershom=13
!  repl rrate with 13
!  skipto="QPOST1"
! case qpershom=22
!  repl rrate with 22
!*  if letter=1.and.qpershom=22
!*   skipto="QREMLET2"
!*  else
!   skipto="QENDBIT"
!*  endif
! case qpershom=14
!  repl rrate witH 14
!  do langcob
!  skipto="QENDBIT"
! case qpershom=2
!  skipto="RRATE4"
!endcase
-----------------------
IF rrate<>1 .and. rrate<>3.and. qpershom=2
!if qhsize<>0.or.qsposit<>0
!xpext=" "
!xpos=" "
!do case
! case ragepos=1
!  xpext=""
! case ragepos=2
!  xpext="second "
! case ragepos=3
!  xpext="third "
! case ragepos>3
!  xpext=str(ragepos,1)+"th "
!endcase
!if ragepos=1.and.(qhsize=1.or.qhsize=23)
! xpos="The only person aged 18 or over"
```

```
!else
! if ragepos>0.and.ragepos<10.and.qhsize>1.and.qhsize<10
!  xpos="The "+UPPER(xpext)+"oldest person"
! else
!  xpos="UNKNOWN POSITION"
! endif
!endif
!else
! xpos="AS ON CALL SHEET"
!endif
```

When would be the best time to call back to speak to this person?

[INTERVIEWER: WRITE RESPONDENT'S HOUSEHOLD AGE-POSITION ON CALLSHEET]

```
ÚÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄ
    ³ SELECTED RESPONDENT IS: "+XPOS+"

ÀÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄÄ
```

RECORD ON THE LOG SHEET.

[INTERVIEWER: OFFER FREECALL IF HOUSEHOLD REFUSAL]

```
#   44. CALLBACK ARRANGED (FOR A TIME WITHIN THE SURVEY PERIOD)
   [13. REQUIRE LETTER TO CONTINUE]
    22. HOUSEHOLD REFUSAL
    66. PERSON UNAVAILABLE FOR REST OF SURVEY PERIOD
     6. PERSON UNSUITABLE - EXPLAIN IN COMMENTS
-------------------
rrate4,n,2,0,44,44,22,66,6,13
!if rrate4=13
! replace rrate with rrate4
! skipto="QPOST1"
!else
! repl rrate with rrate4
```

```
! skipto="QENDBIT"
!endif
------------------
IF rrate<>1 .and. rrate<>3
!if qpershom=1
WHEN REQUIRED PERSON IS ON PHONE ASK
Good morning/afternoon/evening, are you [SELECTED RESPONDENT]?
My name is _____. I'm calling on behalf of the Faculty of
Medicine at
the University of New South Wales.
!endif
```

We'd like to invite you to participate in a study on public views
about mental
illness. We only want your opinion. There are no right or wrong
answers.

This involves completing a short and completely confidential
telephone survey.
We don't need to know your name or address and the telephone number
we called
you on will not be linked to your answers.

```
#   [1. CONTINUE   2. RESPONDENT OFFERED LETTER]
    [4. Not Now SPOKE TO RESPONDENT - CALLBACK ARRANGED]
```

I can tell you briefly about the study now, OR we have an information
letter
that describes the study. We can send this letter to any address you
nominate.

[INTERVIEWER: CLARIFY IF NECESSARY, 'It doesn't have to be your home
address.']

```
---------------
qsend,n,1,0,1,2,4
!if qsend=2
```

```
! skipto="qpost1"
! repla rrate with 13
!else
! if qsend=4
!  repla rrate with 4
!  SKIPTO="QENDBIT"
! else
!  repla rrate with 0
! endif
!endif
---------------
!*INFORMATION
INTERVIEWER: READ SECTIONS OR ALL THE LETTER IN ADDITION IF NECESSARY
```

We would like to ask your views on the causes of mental illnesses.

Only the research team will see your answers, no information
identifying you
will be gathered and answers used in publications will be grouped so
there is
no possibility that individuals can be recognised. The interview
will take
most people around 15 minutes to complete.

Can you help us with this interview?
Would now be a good time?

```
#  [INTERVIEWER: IF RESPONDENT REFUSES, OFFER FREECALL]
    0. or 1. PROCEED
    2. NO - REFUSAL  [13. SEND LETTER]
    4. Not Now SPOKE TO RESPONDENT - CALLBACK ARRANGED
    6. RESPONDENT UNSUITABLE (EXPLAIN IN COMMENTS)
    66. RESPONDENT UNAVAILABLE FOR SURVEY PERIOD (COMMENTS)
    14. LANGUAGE PROBLEM   8. NOT IN AREA
```

  [HVRF CONTACT: Norma Taylor - Study supervisor - Freecall 1800 355
534]

```
----------------
rrate3,n,2,0,0,2,4,6,8,13,14,66
!repl rrate3 with iif(rrate3=1,0,rrate3)
!if rrate3>1
! repl rrate with rrate3
! if rrate3=2
!  skipto="QENDBIT"
!   repla rrate with 2
! else
!  skipto="QENDBIT"
!   if rrate3=14
!    repl rrate with 14
!    do langcob
!   endif
!   if rrate3=13
!    replace rrate with rrate3
!    skipto="QPOST1"
!   endif
!  endif
!else
! if at(str(rrate,3),"  1  3 17")=0
!   repl rrate with 0
! endif
! if .not.ck()
!  repl rsave with 1
! endif
!endif
!if len(rtrim(scale))<20
! iiz=0
! iix=0
! for iiz=1 to 20
!  iix=mod(int(random(id+iiz)*1000000),2)
!  replace scale with rtrim(scale)+ltrim(str(iix+1))
! next
!endif
------------------
```

IF

qnolet1=13.or.QHSIZE=13.OR.rrate3=13.OR.rrate=13.OR.qsend=2.OR.RRATE4
=13.OR.QPERSHOM=13.OR.QPERS=13

WHAT TYPE OF CONTACT?

\#   [2. SEND LETTER 3. SEND FAX 4. SEND E-MAIL]

[HVRF CONTACT: Norma Taylor/Vivienne Lunn - Supervisors - Freecall
1800 355 534]

!*   [IF PHONE]   Can I call back tomorrow or the next day...?
   [IF FAX/E-MAIL]   I'll arrange for the letter to be sent and call
back
                      [E-MAILS SENT NEXT DAY]

 [IF LETTER] Record the following details:

 [INTERVIEWER - USE The Householder/First Name if offered- DO NOT USE
SURNAME]
NAME   \#

ADDRESS \#

SUBURB   \#
                                [set CAPS LOCK OFF]
POSTCODE \#   E-MAIL \#

FAX   \#
[IF LETTER]
    I'll call back in a few days after you have received the letter
----
qpost1,n,1,0,2,4
qpost1n,c,60,0
qpost1a,c,60,0
qpost1s,c,40,0
qpost1p,c,4,0
qpost1e,c,40,0
qfax1,c,12,0

```
!if qpost1>1
! replace rrate with 13
!else
! replace rrate with 4
!endif
!skipto="QENDBIT"
---------------
```

Thank you for agreeing to be part of our study. If you need to stop at any time
let me know. If you don't want to answer any question say so and I'll move on
to the next one.

Before we begin I will explain the terms we are using:

The mental illnesses referred to are schizophrenia, bipolar disorder and
depression.

SCHIZOPHRENIA is a mental illness characterised by loss of touch with
reality and may include hallucinations and delusions.

As you may know, BIPOLAR DISORDER, previously known as manic depression,
is a mood disorder with periods of both depression and elevated mood
or mania.

By DEPRESSION we mean more than normal sadness; we mean a clinical depression
severe enough to interfere with daily functioning.


```
# <Enter> to continue
-------------
qintro,n,1,0
-------------
!RANDOM
```

I'm now going to read a list of factors that might cause a mental illness.
Not all of them are equally important. Please tell me how important you think
each of these factors is as a cause of mental illness.

[INTERVIEWER: READ QUESTION WITH FIRST ITEM - THEN READ SCALE AS PRESENTED
             - DO NOT READ NUMBERS - RE-READ SCALE AS NECESSARY]

    "+iif(substr(scale,1,1)="1","1. Not important at all","5. Very important   ")+"
    "+iif(substr(scale,1,1)="1","2. Of little importance","4. Important   ")+"
    3. Moderately Important
    "+iif(substr(scale,1,1)="1","4. Important   ","2. Of little importance")+"
    "+iif(substr(scale,1,1)="1","5. Very important   ","1. Not important at all")+"
                                        8. DON'T KNOW [DO NOT READ OUT]
                                        9. REFUSED   [DO NOT READ OUT]

q1. How important is ... [READ ITEM] ... as a cause of mental illness?

Genetics
Accumulation of daily life stresses
Imbalance of chemicals in the brain
Major life changes
Being in a difficult relationship or marriage
Personality flaws
A Difficult or abusive childhood
Sexual abuse
Recreational drug abuse
Family environment
Parental behaviour
Bad luck

```
----------------------
q1p,n,1,0,1,5,8,9
----------------------
!RANDOM
```

q2. How strongly do you agree or disagree with the following
statements:

[INTERVIEWER: READ FIRST STATEMENT - THEN READ SCALE AS PRESENTED
             - DO NOT READ NUMBERS - RE-READ SCALE AS NECESSARY]

```
    [READ ITEMS AS PRESENTED - DO NOT READ NUMBERS]
    "+iif(substr(scale,2,1)="1","1. Strongly disagree","5. Strongly
agree   ")+"
    "+iif(substr(scale,2,1)="1","2. Disagree         ","4. Agree
")+"
    3. Neither agree nor disagree
    "+iif(substr(scale,2,1)="1","4. Agree            ","2. Disagree
")+"
    "+iif(substr(scale,2,1)="1","5. Strongly agree   ","1. Strongly
disagree")+"
```

                                    8. DON'T KNOW [DO NOT READ OUT]
                                    9. REFUSED   [DO NOT READ OUT]

\# Mental illnesses are caused by an interplay of genetic risk and
stressful
    life experiences.

\# It is possible to have a genetic risk for a mental illness but
never
    actually get the disorder.

\# It is possible to have a mental illness without a genetic risk.

```
--------------------
q2p,n,1,0,1,5,8,9
--------------------
!RANDOM
```

In the next question we use the term 'stigma', meaning 'shame' or 'disgrace'.

q3. If there was evidence that mental illnesses were caused in part by the

    genes you inherit, how would this affect stigma attached to these disorders?

    Do you think .....   [READ ITEMS AS PRESENTED - ENTER 1 FOR SELECTION]

    [8. DON'T KNOW]

Stigma would increase

Stigma would decrease

A genetic basis for a mental illness would make no difference to stigma

```
------------------
q3p,n,1,0,0,1,8
------------------
!if q3p1+q3p2+q3p3=0
! skipto="-q3p"
!endif

!if (q3p1=1.and.q3p2=1).or.(q3p1=1.and.q3p3=1).or.(q3p2=1.and.q3p3=1)
INTERVIEWER: MULTIPLE YES RESPONSES
.
! skipto="-q3p"
!WAIT
!endif
------------------
```

q3say,s,0,0

[INTERVIEWER: READ DEFINITION REMINDER TEXT]

For the following questions we use depression as a real life example.

As before, by 'depression' we mean 'a clinical depression severe enough to

interfere with daily functioning'.

.

!WAIT

----

qdef2,s,0,0

!RANDOM

q4p. There is a genetic test that can predict a person's risk of developing

    depression if stressful life events occur. The test shows whether a

    person's risk of depression is higher, lower or the same as that of an

    average person.

Compared with the average person, would you say your risk of

depression is...

    [READ ITEMS AS PRESENTED - ENTER 1 FOR SELECTION]

                                    [8. DON'T KNOW]

Higher than average

   (prompt - that is, more likely to develop depression than the

average person)

Lower than average

   (prompt - that is, less likely to develop depression than the

average person)

```
#  The same as the average person


---------------
q4p,n,1,0,0,1,8
---------------
!if q4p1+q4p2+q4p3=0
! skipto="-q4p"
!endif


!if (q4p1=1.and.q4p2=1).or.(q4p1=1.and.q4p3=1).or.(q4p2=1.and.q4p3=1)
INTERVIEWER: MULTIPLE YES RESPONSES
.
! skipto="-q4p"
!WAIT
!endif
------------------
q4say,s,0,0
------------------


q5. If a genetic test to determine your risk for developing
depression was
    available directly to you using the internet to access the test,
would
    you be interested in having it?


    [IF ASKED SAY: 'It would involve sending a saliva sample to a
genetic
                      testing company in a special kit they provide'.]


    [READ ITEMS AS PRESENTED - DO NOT READ NUMBERS]
#   "+iif(substr(scale,3,1)="1","1. No, definitely not","4. Yes,
definitely   ")+"
    "+iif(substr(scale,3,1)="1","2. No, probably not  ","3. Yes,
probably      ")+"
```

```
    "+iif(substr(scale,3,1)="1","3. Yes, probably     ","2. No,
probably not  ")+"
    "+iif(substr(scale,3,1)="1","4. Yes, definitely   ","1. No,
definitely not")+"
```

    [DO NOT READ OUT   5. DON'T USE INTERNET   8. DON'T KNOW 9.
REFUSED]

----
q5,n,1,0,1,5,8,9
----

q6. If a genetic test to determine your risk for developing
depression
    was available through your own doctor, would you be interested in
having
    it?

    [READ ITEMS AS PRESENTED - DO NOT READ NUMBERS]
```
#   "+iif(substr(scale,3,1)="1","1. No, definitely not","4. Yes,
definitely    ")+"
    "+iif(substr(scale,3,1)="1","2. No, probably not  ","3. Yes,
probably      ")+"
    "+iif(substr(scale,3,1)="1","3. Yes, probably     ","2. No,
probably not  ")+"
    "+iif(substr(scale,3,1)="1","4. Yes, definitely   ","1. No,
definitely not")+"
```

                                        8. DON'T KNOW [DO NOT READ OUT]
                                        9. REFUSED   [DO NOT READ OUT]

----
q6,n,1,0,1,4,8,9

!RANDOM
q7. Irrespective of your previous two answers, if a genetic test for
determining

your risk for developing depression was available from your
doctor, how
strongly would you agree or disagree to having the GENETIC TEST
FOR
DEPRESSION ... [READ FIRST ITEM - THEN READ SCALE AS PRESENTED]

"+iif(substr(scale,2,1)="1","1. Strongly disagree","5. Strongly
agree   ")+"
"+iif(substr(scale,2,1)="1","2. Disagree   ","4. Agree
")+"
3. Neither agree nor disagree
"+iif(substr(scale,2,1)="1","4. Agree   ","2. Disagree
")+"
"+iif(substr(scale,2,1)="1","5. Strongly agree   ","1. Strongly
disagree")+"
                                8. DON'T KNOW [DO NOT READ OUT]
                                9. REFUSED   [DO NOT READ OUT]

IF a mental illness ran in your family.

IF your doctor recommended it.

IF the result was 100% certain that you would or would not develop
depression.

IF the result couldn't be used against you when applying for
insurance or
  employment.

----
q7p,n,1,0,1,5,8,9

[INTERVIEWER: READ DEFINITION REMINDER TEXT]

Again, in the next questions 'depression' still means: 'a clinical
depression
severe enough to interfere with daily functioning'.

```
.
!WAIT
------------------
qdef3,s,0,0
------------------
!RANDOM
```

q8a. How strongly do you agree or disagree with the following potential benefits

    or disadvantages of knowing your genetic risk for developing depression?

If the genetic test showed you were at INCREASED RISK of depression: [READ FIRST

 STATEMENT - THEN SCALE - RE READ If the genetic ... AFTER 4th STATEMENT]

              [READ ITEMS AS PRESENTED - DO NOT READ NUMBERS]

Do you...

 "+iif(substr(scale,2,1)="1","1.Strongly disagree 2.Disagree 3.Neither D/A 4.Agree 5.Strongly Agree" ,"5.Strongly agree 4.Agree 3.Neither A/D 2.Disagree 1.Strongly Disagree")+"

   [DO NOT READ OUT   7. NOT APPLICABLE   8. DON'T KNOW   9. REFUSED]

\# You would be ready to get early psychological help.

\# You would be able to start to minimise stress factors in your life.

\# You may be more likely to feel depressed.

\# You would be afraid of being labelled or stigmatised.

\# You would be afraid of being discriminated against by insurance companies

   or employers.

\# You would start worrying about something that may never develop.

\# You would worry the result might not stay private

----

q8a,n,1,0,1,5,7,8,9

!RANDOM

q8b. How strongly do you agree or disagree with the following potential benefits

    or disadvantages of knowing your genetic risk for developing depression?

If the genetic test showed you had a LOWER RISK of depression: [READ FIRST

 STATEMENT - THEN SCALE - REFRESH IF NECESSARY]

          [READ ITEMS AS PRESENTED - DO NOT READ NUMBERS]
Do you... "+iif(substr(scale,2,1)="1","1. Strongly disagree","5. Strongly agree   ")+"
          "+iif(substr(scale,2,1)="1","2. Disagree   ","4. Agree   ")+"
          3. Neither agree nor disagree
          "+iif(substr(scale,2,1)="1","4. Agree   ","2. Disagree   ")+"
          "+iif(substr(scale,2,1)="1","5. Strongly agree   ","1. Strongly disagree")+"
                    7. NOT APPLICABLE   8. DON'T KNOW [DO NOT READ OUT]
                                          9. REFUSED   [DO NOT READ OUT]

\# You could get peace of mind.

\# You would see yourself as being resilient to depression regardless of any

    stresses in your life.

```
------------------
q8b,n,1,0,1,5,7,8,9
------------------
!RANDOM
q8c. How strongly do you agree or disagree that GENETIC RISK TESTING
for
depression could: [READ FIRST STATEMENT - THEN SCALE - REFRESH IF
NECESSARY]


          [READ ITEMS AS PRESENTED - DO NOT READ NUMBERS]
Do you... "+iif(substr(scale,2,1)="1","1. Strongly disagree","5.
Strongly agree   ")+"
          "+iif(substr(scale,2,1)="1","2. Disagree          ","4.
Agree           ")+"
          3. Neither agree nor disagree
          "+iif(substr(scale,2,1)="1","4. Agree             ","2.
Disagree         ")+"
          "+iif(substr(scale,2,1)="1","5. Strongly agree   ","1.
Strongly disagree")+"
                    7. NOT APPLICABLE     8. DON'T KNOW [DO NOT READ
OUT]
                                          9. REFUSED    [DO NOT READ
OUT]


#  Tell you what treatment might be most effective for you

#  Help legitimise depression as a biological disorder.

#  Trigger a mental illness just by knowing you might have an
increased risk

------------------
q8c,n,1,0,1,5,7,8,9
------------------
!q6txt=" "
!do case
```

```
! case q6=1
! q6txt="would definitely not"
! case q6=2
! q6txt="would probably not"
! case q6=3
! q6txt="would probably"
! case q6=4
! q6txt="would definitely"
! case q6=8
! q6txt="didn't know if you would"
! case q6=9
! q6txt="didn't say if you would"
! case q6=1
!endcase
!repla q9txt6 with q6txt
!q5txt=" "
!do case
! case q5=1
! q5txt="would definitely not"
! case q5=2
! q5txt="would probably not"
! case q5=3
! q5txt="would probably"
! case q5=4
! q5txt="would definitely"
! case q5=8
! q5txt="didn't know if you would"
! case q5=9
! q5txt="didn't say if you would"
! case q5=1
!endcase
!repla q9txt5 with q5txt
----------------
q6text,s,0,0
----------------
You previously said you "+rtrim(q9txt6)+"
```

have the genetic test through your doctor to determine your risk for
developing

depression.

q9a. Now you have thought about some of the positive and negative
implications,
      would you have the genetic risk test for depression now, THROUGH
YOUR
      DOCTOR?

      [READ ITEMS AS PRESENTED - DO NOT READ NUMBERS]
"+iif(substr(scale,3,1)="1","1. No, definitely not","4. Yes,
definitely   ")+"
     "+iif(substr(scale,3,1)="1","2. No, probably not ","3. Yes,
probably   ")+"
     "+iif(substr(scale,3,1)="1","3. Yes, probably   ","2. No,
probably not ")+"
     "+iif(substr(scale,3,1)="1","4. Yes, definitely   ","1. No,
definitely not")+"

                                    8. DON'T KNOW [DO NOT READ OUT]
                                    9. REFUSED   [DO NOT READ OUT]

!if id>100000
#   #
!endif
----
q9a,n,1,0,1,4,8,9
q9txt5,c,30,0
q9txt6,c,30,0

!if q5<>5
And you said you "+rtrim(q9txt5)+" have the genetic test for
depression via
the internet.
!else

Although you previously said you do not use the internet,
!endif

q9b. Now you have thought about some of the positive and negative
implications,
    would you have the genetic risk test for depression now, THROUGH
THE
    INTERNET?

    [READ ITEMS AS PRESENTED - DO NOT READ NUMBERS]
"+iif(substr(scale,3,1)="1","1. No, definitely not","4. Yes,
definitely   ")+"
    "+iif(substr(scale,3,1)="1","2. No, probably not ","3. Yes,
probably   ")+"
    "+iif(substr(scale,3,1)="1","3. Yes, probably   ","2. No,
probably not ")+"
    "+iif(substr(scale,3,1)="1","4. Yes, definitely   ","1. No,
definitely not")+"

    [DO NOT READ OUT   8. DON'T KNOW 9. REFUSED]
!if Q5=5
    [DO NOT READ OUT 5. WOULD NOT USE INTERNET
!endif
----
q9b,n,1,0,1,5,8,9
if q9b=5 .and. q5<>5 skipto q9b

!RANDOM
q10. If you were found through genetic testing to have an increased
risk for
    depression in the event of stress, how much do you agree or
disagree
    with the following possible changes you might make to your
lifestyle?

    [READ FIRST STATEMENT - THEN SCALE - REFRESH AS NECESSARY]

```
        [READ ITEMS AS PRESENTED - DO NOT READ NUMBERS]
Do you...  "+iif(substr(scale,2,1)="1","1. Strongly disagree","5.
Strongly agree   ")+"
        "+iif(substr(scale,2,1)="1","2. Disagree         ","4.
Agree          ")+"
        3. Neither agree nor disagree
        "+iif(substr(scale,2,1)="1","4. Agree            ","2.
Disagree       ")+"
        "+iif(substr(scale,2,1)="1","5. Strongly agree   ","1.
Strongly disagree")+"
                  7. NOT APPLICABLE     8. DON'T KNOW [DO NOT READ
OUT]

                                        9. REFUSED    [DO NOT READ
OUT]
```

You would start therapies or courses that would help you learn to develop

    better strategies to cope with stress.

You would modify potential stressors in your life such as stressful job,

    relationship or domestic situations.

You would reduce excessive drug or alcohol use.

You would help your children learn how to be more resilient to stress in case

    they were also at increased risk for depression.

You would decide not to have children

You would do nothing - you would not be at risk for depression regardless of

    what life throws at you.

You would do nothing - no point in worrying about something that may not

    develop.

----

q10p,n,1,0,1,5,7,8,9

Because answers may vary according to whether someone has experienced a mental
illness themselves or through the experience of family or friends, it would be
helpful if we knew a little about your own experience of mental illness.
Remember that everything you say is confidential and there is no obligation
to answer any question you don't want to.

q11a. Has any CLOSE relative or CLOSE friend ever been diagnosed with
    depression, bipolar disorder or schizophrenia?

[1. YES 2. NO 8. DON'T KNOW 9. REFUSED]

[INTERVIEWER - RELATIVE CAN BE BIOLOGICAL, ADOPTED, or PARTNER]

----

q11a,n,1,0,1,2,8,9

----

q11c. Have you ever been diagnosed with depression or bipolar disorder
    or schizophrenia?

[1. YES 2. NO 8. DON'T KNOW 9. REFUSED]

----

q11c,n,1,0,1,2,8,9

I'd now like to ask some general questions about you, to make sure we've

interviewed a wide range of people.

qdem1. Gender?

\# [M. Male F. Female - INTERVIEWER OBSERVE - DO NOT ASK]

qdem2. In what year were you born?

\#   [YEAR: RANGE 1900 - 1990? - 8888. DON'T KNOW 9999. REFUSED]

        [IF REFUSED, OFFER RANGE OF AGES]

        [PROMPT WITH AGE GROUPS IF WON'T GIVE ACTUAL YEAR]
\#   101. 18-19   103. 30-39   105. 50-59   107. 70+
          102. 20-29   104. 40-49   106. 60-69

        [888. INELIGIBLE AGE: Page Up and exit - 999. REFUSED]

----
qdem1,c,1,0,valid upper(qdem1)="M".or.upper(qdem1)="F"
qdem2,n,4,0,1910,1990,8888,9999
qdem2r,n,3,0,101,107,999,888,0
if (qdem2=9999.or.qdem2=8888).and.qdem2r=0 skipto qdem1
----

qdem3c. In which country were you born?

        1.   Australia   15.   Malaysia
        2.   China (excl. Taiwan) 16.   Malta
        3.   Cyprus   17.   New Zealand
        4.   Egypt   18.   Philippines
        5.   Fiji   19.   Portugal

6.	Germany	20.	South Africa
7.	Greece	21.	UK and Ireland
8.	Hong Kong	22.	USA
9.	India	23.	Viet Nam
10.	Indonesia/Timor	24.	Former Yugoslavia
11.	Italy		
12.	Japan		
13.	Korea		
14.	Lebanon		

```
    [TYPE IN OTHER RESPONSES - 88. DON'T KNOW  99. REFUSED]
#
------------------
qdem3c,c,60,0,0,24,88,99
------------------
```

qdem4. What is your highest educational qualification?

```
    [PAUSE, AND PROMPT IF NECESSARY. ENTER ONE ONLY]
#   1. No formal schooling
    2. Primary school
    3. Lower secondary school/School certificate/Intermediate
Certificate
    4. Technical or trade certificate
    5. Higher secondary school/ HSC/VCE/Leaving Certificate
    6. College certificate/diploma
    7. Undergraduate degree [Queried: University degree]
    8. Postgraduate degree  [Queried: University degree]

    88. DON'T KNOW
    99. REFUSED

----------------
qdem4,n,2,0,1,8,88,99
----------------
IF qdem4=7.or.qdem4=8
```

qdem5. What was the main area you studied at a tertiary level?

    [TYPE IN RESPONSE - 99. REFUSED]
#

----
qdem5,c,80,0,0,0,99
----

qdem6. Are you currently in paid employment?

[1. YES 2. NO 8. NOT SURE/DON'T KNOW 9. REFUSED]

----
qdem6,n,1,0,1,2,8,9

IF qdem6=2

qdem8. Are you ...

    [READ ITEMS]
1. Looking for work
    2. Retired
    3. Undertaking home duties
    4. A non-working student
    5. Permanently ill or unable to work

    6. NEVER WORKED [DO NOT READ]

    9. REFUSED

----
qdem8,n,1,0,1,6,9

IF qdem6=1 .or. (qdem6=2 .and. qdem8=2)

qdem9. "+iif(qdem6=1,"In your main job, what has been your occupation in the last 12 months","Before you retired what was your main occupation")+";

    a broad description will do?

    [PROBE FOR INFORMATION ALLOWING ASCO CODING]

     [PAUSE: READ ONLY IF NECESSARY]
  1. Manager or Administrator
  2. Professional
  3. Associate professional
  4. Tradesperson and related
  5. Advanced clerical and service
  6. Intermediate clerical, sales, and service
  7. Intermediate production and transport
  8. Elementary clerical, sales, and service
  9. Labourer And Related

  20. NEVER WORKED [DO NOT READ]

  [TYPE IN OTHER - 99. REFUSED]

```
#
------------------
qdem9,c,60,0,0,9,99
------------------
IF qdem6=2 .and. qhsize<>1
```

qdem9a. What are the occupations of other family members of your household who

    are over 18; just a broad description of those currently working will do?

    [PROBE FOR INFORMATION ALLOWING ASCO CODING - EXCLUDE HOUSE MATES]

    [PAUSE: READ ONLY IF NECESSARY]
  1. Manager or Administrator
  2. Professional
  3. Associate professional

4. Tradesperson and related

5. Advanced clerical and service

6. Intermediate clerical, sales, and service

7. Intermediate production and transport

8. Elementary clerical, sales, and service

9. Labourer And Related

[TYPE IN OTHER - 88. DON'T KNOW 99. REFUSED]

#

#

#

#
----
qdem9a1,c,60,0,0,9,88,99
qdem9a2,c,60,0,0,9,0,88,99,0
qdem9a3,c,60,0,0,9,0,88,99,0
qdem9a4,c,60,0,0,9,0,88,99,0
----

qdem10. What is your marital status?

[DO NOT READ ITEMS UNLESS RESPONDENT HESITATES]
1. Married/de facto

2. Single

3. Divorced

4. Separated but not divorced

5. Widowed

8. DON'T KNOW/NOT SURE

9. REFUSED

----
qdem10,n,1,0,1,5,8,9
----

qdem15. Could you tell me your postcode?

[NUMBER: Range 0000 - 8777;   8888. DON'T KNOW 9999. REFUSED]

----
qdem15,cn,4,0,0000,8777,8888,9999

If you are interested in the results of this study, we will include
the
information on the Black Dog Institute website in about 3 to 6 months
time.
The website address is www.blackdoginstitute.org.au and go to the
depression
page.

Would you be willing to be contacted about participating in future
research
about attitudes towards genetics and mental illness?

I remind you again that the answers you have given today are
anonymous and if
you are interested in participating in further research we would need
to take
your name and address. Your contact details will be protected with an
encrypted
identification code, so that your survey responses cannot be linked
to your
identifying details.

Will you give us a name and address so we can send you information
about this?
It might be about 12 months before we contact you.

[1. YES 2. NO]

[INTERVIEWER - IF ASKED WHAT RESEARCH - SAY .... I am only involved in data

collection at this stage of the study and the researchers have not revealed

what the later stage is about. You can agree now and opt out later.

]

----
qcons,n,1,0,1,2

IF qcons=1

  [TYPE IN NAME - FIRST NAME SUFFICIENT?]
#

  [FLAT/UNIT NUMBER]
#
  [STREET NUMBER]
#
  [STREET NAME]
#
  [SUBURB]
#
  [POSTCODE]
#
----
qname,c,60,0
qunit,c,20,0
qstno,c,30,0
qstreet,c,40,0
qsuburb,c,40,0
qpostc,cn,4,0,0000,8777,8888,9999

!if id=-999
This is the first time we have used this questionnaire. Do you have any comment

on any of the questions, or the questionnaire as a whole?

```
   [TYPE IN COMMENT - 22. NO COMMENT  99. REFUSED]
#
!endif
Thank you for participating in this survey.  For further information
about
depression and bipolar disorder visit beyond blue's website at
www.beyondblue.org.au or call their info line on 1300 224 636. You
can also
visit the Black Dog Institute website at www.blackdoginstitute.org.au
If the interview has raised any distressing issues for you now, or in
the
future, please call Lifeline on 13 1114.

[HVRF CONTACT: Norma Taylor/Vivienne Lunn - Supervisors - Freecall
1800 355 534]

# <Enter> to Finish
--------------
qques,c,160,0,0,0,22,99
qendsum,n,1,0
skipto QENDBIT
--------------
#


----------------
scale,c,20,0
----------------
```

B.2 – INTERVIEWER TRAINING MANUAL

Survey of mental illness
School of Psychiatry, University of NSW

Instructions for Conducting Interviews

HVRF Ref No: 519/2008

Background

Our Client

School of Psychiatry, University of NSW

Client Contact

Primary contact

Alex Wilde

School of Psychiatry

Faculty of Medicine

UNSW (Kensington Campus)

Tel: 02 9382 8511

Mob: 0409 607 125

Email: alex.wilde@unsw.edu.au

Mailing address:

Room G22

Black Dog Institute

Hospital Road

Prince of Wales Hospital

Randwick, NSW, 2031

HVRF Staff

Project Manager: Andrew Searles (ext. 525)

CATI Programmer: David Shellard (ext. 518)

Survey Supervisor: Vivienne Lunn and Norma Taylor??? (ext. 538)

Team Leader: Terrie Brownee (ext. 546)

Background

Identification of genes that suggest susceptibility to psychiatric illness present an opportunity to predict which individuals might be 'at increased risk' of developing a mental illness such as depression, bipolar disorder or schizophrenia. It may then be possible to reduce burden of disease from mental disorders through intervention strategies at a presymptomatic stage. At present no definitive genetic tests are available. However, as research into candidate genes and gene-environment interactions involved in major depression, bipolar disorder and schizophrenia rapidly advances, there is likely to be an associated demand for genetic counselling and testing. Successful interventions based on genetic risk depend on public understanding of and attitudes towards complexity of risk prediction involving susceptibility genes and gene-environment interactions. Evaluating public interest in and perceptions about genetic risk testing, using depression as an example, will inform genetic counselling services and assist medical services to gauge potential uptake of future molecular-based interventions in mental health.

Aims of the study

This study aims to:

- **Describe public attitudes towards future genetic risk testing** for clinical depression in the light of their beliefs about the causes of mental illness, and the perceived contribution of genetic and environmental factors.

- **Identify public perceptions of ethical and social implications of genetic testing in psychiatry** and

- **How these perceptions impact on interest in genetic testing** for clinical depression.

- **Describe how public understanding of psychiatric genetics affects perceived stigma and the potential for discrimination,** which in turn impacts on uptake of mental health services.

Researchers

Alex Wilde

A/Prof Bettina Meiser

Prof Phillip Mitchell

Prof Peter Schofield

Study Aim (HVRF perspective)

To: Conduct a computer assisted telephone interview (CATI) amongst a randomly selected group of householders in Australia. Participants in this survey:

(1) Will be contacted using phone numbers generated by random digit dialing
(2) Be selected randomly from within the household
(3) Will be asked to complete the CATI interview
(4) Be asked to provide consent to be included in the next phase of the study at the end of the survey.

Methods

Study design	▪ Cross sectional (from HVRF perspective) but it is in a longitudinal study – participants in the first survey will be asked for their permission to be contacted about further research into mental illness and genetics.
Sampling frame	▪ Random digit dialling. ▪ National. ▪ These contacts will include silent and unlisted households.
Pilots	▪ Two pilots were completed. After pilot 1, some difficult questions were simplified and re-worded. ▪ As per most surveys, during the pilot some participants found the questionnaire difficult. ▪ As always, if the participant does not understand the question re-read it. If the participant still does not understand / cannot / will not answered code as don't know or refused (as appropriate).
The Respondent	▪ To be ___*randomly*___ selected from eligible participants in the household. Follow the CATI prompts for the selection process.
Completed interviews	▪ The number of participants is 1,000.
Interview duration	▪ Estimated interview duration is about 15 minutes
Interviewing times	▪ Between 9 a.m. and 8.30 p.m. on weekdays. ▪ Variation in these times will be made based on times differences across Australia –your Supervisors and Team Leader will make these variations as needed. ▪ Supervisors will assess call outcomes to determine whether weekend call attempts are needed.

Call attempts	• *A minimum of 6 call attempts will be used to contact the household and identify the respondent.*
	• *Once this contact is identified up to a further five calls will be made to complete the interview.*
	• This allows sufficient call attempts to book interview times and to make successive calls to participants who may be otherwise difficult to contact.
	• All call attempts will be logged in the CATI system and provided to the client. Call attempts will be made on different days and at different times so that contact opportunities with each household are maximised.
	• *If the first four consecutive calls to a telephone number result in contact with a fax machine or data line*, this will be recorded and no further call attempts will be made. These calls must have been made on different days and at different times.
	• Please record each call attempt both on the call sheet and on the CATI screen, so they both correspond.
	• Please ensure booked appointments are recorded on the interviewing appointment schedule provided with call sheets.
	• The interviewing appointment schedule for call backs will provide you with 'preferred appointment' times – you should always attempt to make booking in these times. If this is not possible, alternatives must be discussed with your Supervisors / Team Leader to ensure someone is available to phone at the appointed time.
	• Use the 1800 free call number on the answering machine messages. *A maximum of 3 messages* can be left for any single participant. Only one message can be left on any single day. Messages can be left on the first phone call.

Study issues	**An information letter is available:**
	o This letter is primarily for households where the phone answerer is hesitant about participation and/or the authenticity of the survey.
	o If a letter is requested, CATI will prompt you to record the details.
	o Additionally - fill in the "letter sheet" providing the id, name (or "householder") and mailing address. These sheets will be collected each night.
	o Letters will be prepared for the next day's post.
	o A return phone will be scheduled about 5 working days after the letter is posted.
	We are recruiting at the end of the study
	o All participants are asked for their permission to be contacted again in the future about this research.
	o Those who agree will be asked to provide their name and address.

Data Collection Issues

Timelines

Main study: Six weeks (25 June 2008)

Dealing with refusals

The HVRF has a number of strategies to help increase study response rates. These strategies are described in more detail in the HVRF Telephone Interviewing Protocols (see pages 21-22) and in Module 2 of HVRF Interviewer Training Manual (see page 12).

Keep the interview moving!

Be in control of the interview. Do not encourage conversations with respondents or householders.

Bias

The conduct of any interview has the potential to introduce bias. It is critical that a professional interview technique be maintained. This does not prevent friendly and polite greetings – but it does require reading the CATI script exactly as written and only providing prompts that are provided on the CATI screen.

Measurement bias can be introduced if interviewers vigorously prompt on some questions but not others, or some interviewers vigorously prompt but others do not. This bias can seriously affect a study. To prevent this bias …… read the script exactly as written. Please also refer to the HVRF Training Notes *Asking the Questions* Update 16.05.07

Say it as it is!

Stick to the script. Re-phrasing a question may change its meaning and might influence (i.e. "lead") the respondent's answer. Rather, repeat the answer to confirm that the response has been heard correctly.
If a respondent does not understand a question, read it again, rather than paraphrasing it.
Do not let a respondent's manner influence your tone and telephone manner. Talk to each person with the same manner and tone. This applies whether the person you deal with is friendly, rude or angry.

More Information

If the respondent requests more information follow the following instructions:

IF CONCERNS ABOUT THE TELEPHONE CONTACT:
- *Use 1800 HVRF contact and refer them to Vivienne Lunn and/or Norma Taylor*
- *If needed refer participants to:*
  - *Andrew Searles (02 4969 4566 ext 525) but only on Mon / Tue / Wed or*
  - *Jessica Pritchard (02 4969 4566 ext 557) Mon to Fri.*

IF THE RESPONDENT REQUIRES CONTACT INFORMATION RATHER THAN BE CONTACTED BY CLIENT, *SAY***:**
- *If you would like more information and do not wish to be contacted directly, please contact Alex Wilde, from the University of NSW, ask her to phone XXXXXXX.*

B.3 - PARTICIPANT INFORMATION STATEMENT

THE UNIVERSITY OF
NEW SOUTH WALES

PROFESSOR
PHILIP MITCHELL

HEAD
School of Psychiatry

13 May 2008

Ethics approval no: HREC 08098

THE UNIVERSITY OF NSW
PARTICIPANT INFORMATION

Title of project: 'Psychosocial implications of genetic risk information about mental illness'

I am contacting you today to invite you to participate in a research study about genetics and mental illness. You were randomly selected for potential participation by random telephone dialing.

The aim of the study is to find out more about the public's understanding of the role of genes in the development of mental illness and attitudes towards future genetic testing for risk for depression. The information that will be collected as part of this study will be used with the aim of improving mental health care for people with and at risk for psychiatric disorders; reducing stigma associated with psychiatric disorders and informing genetic counseling services involving psychiatric disorders.

Should you decide to participate in this study, an interviewer from Hunter Valley Research Foundation acting on behalf of the University of New South Wales will contact you by telephone. The telephone interview will take approximately 15 minutes. There are no known risks or benefits associated with participation in this study.

The information that you provide will be used solely for the purpose of analysis and will remain confidential and will not be disclosed except with your permission or as required by law. Your contact details will be protected with an encrypted identification code, so that your survey responses cannot be linked to your identifying details. If you give us your permission by taking part in the survey when an interviewer calls you back, we plan to publish the results as an article for submission to a specialist journal and to general publications to ensure that the findings will be disseminated to a wider readership. In any publication, information will be provided in such a way that you cannot be identified.

If you *do not* wish to participate, please let the interviewer know when they call you back. However, your participation in this study would be invaluable and most appreciated. Many thanks for considering our request.

Complaints may be directed to the Ethics Secretariat, University of NSW, Sydney, NSW 2052, Australia, Tel. 02 9385 4234, Fax 02 9385 6648, e-mail: ethics.sec@unsw.edu.au

Your decision whether or not to participate will not prejudice your future relations with the University of New South Wales or your general health care. If you decide to participate, you are free to withdraw your consent and to discontinue participation at any time without prejudice.

If you have any additional questions later, please call the principal researcher Alex Wilde at the University of NSW on 02 9382 8511, who will be happy to answer them. Please note Alex will be away until early July.

Ms Alex Wilde

THE PRINCE OF WALES HOSPITAL
SYDNEY 2031, AUSTRALIA
Telephone + 61 (2) 93823711
Facsimile + 61 (2) 93828151
Email: phil.mitchell@unsw.edu.au
ABN 57 195 873 179

Appendix C – Study Materials from Media Analysis (STUDY 3)

C.1   **Coding Tree of Media Frames**

C.2   **Descriptors of Codes for Media Analysis**

C.1 - CODING TREE OF MEDIA FRAMES

Year, psychiatric disorder, and publication were coded as given and are not shown.

For code descriptors see Appendix C.2.
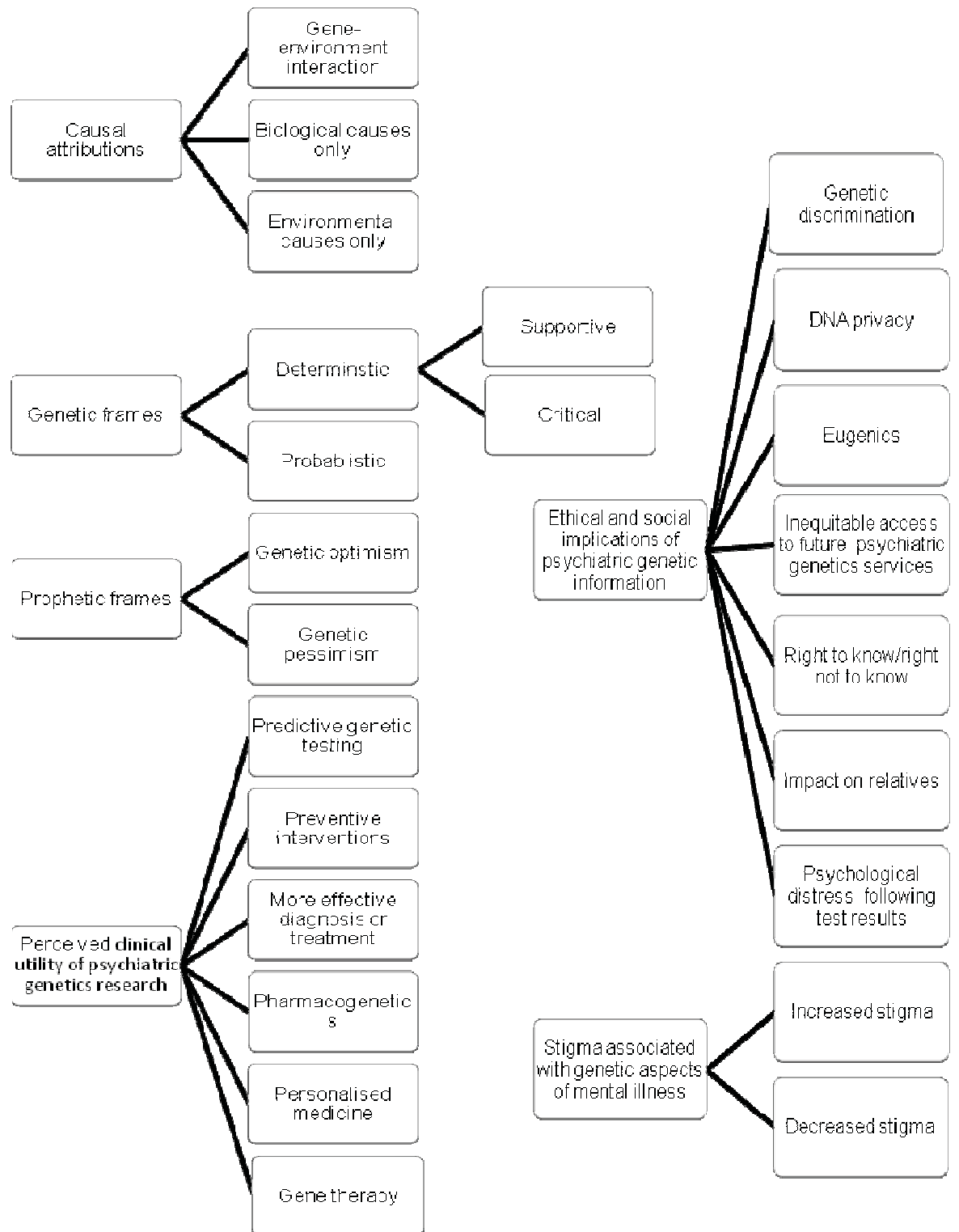
C.2 – DESCRIPTORS OF CODES FOR MEDIA ANALYSIS

- ▪ All statements below refer to the genetics of major depressive disorder, bipolar disorder or schizophrenia.
- ▪ Articles are coded by paragraph except for Coding groups 1 to 3.
- ▪ More than one code may be used for the same paragraph.

CODE	DESCRIPTION
1. Year (14 codes)	**Code whole article according to year (1996-2009).**
2. Psychiatric condition (3 codes)	**Code whole article according to one or more of the three target psychiatric disorders (hereafter referred to as 'disorder').**
2.1 Major depressive disorder	Mentions major depressive disorder/major depression/depression. Excludes 'manic depression' which is coded under bipolar disorder.
2.2 Bipolar disorder	Mentions bipolar disorder (includes mention of 'manic depression').
2.3 Schizophrenia	Mentions schizophrenia or other psychotic disorders.
3. Media publication (15 codes)	**Code whole article according to publication (see Figure 4, page 152 for publications included in the study).**
4. Genetic frames	**How does journalist communicate role of genetic factors?**
4.1 Genetic determinism (2 codes)	**Over emphasis of genetic factors – e.g. implies single gene causes disorder.**
4.1.1 Critical	Critically evaluates deterministic concepts.
4.1.2 Supportive	Supports concepts that suggest genes determine disease. e.g. 'the gene for X is found'.
4.2 Probabilistic (1 code)	Mentions that genetic factors contribute a susceptibility to the risk for a disorder.

CODE	DESCRIPTION
5. Causal attributions (5 codes)	**How does journalist frame causal attributions of mental illness?**
5.1 GxE	Acknowledges a gene by environment effect on the development of a disorder.
5.2 Biological/genetic causes only	Mentions genetic causes or 'chemical imbalance'.
5.3 GxG	Acknowledges the potential role of multiple genes in the development of a disorder.
5.4 Environmental causes only	Mentions cause(s) other than genetic factors.
5.5 May not develop disorder	Acknowledges that presence of gene variant/mutation A may not lead to disorder B (incomplete penetrance). Or makes statements such as 'no genetic basis', 'there is no gene for.....'or 'cause of disorder unknown'.
6. Prophetic frames (4 codes)	**How does journalist communicate social value of psychiatric genetics?**
6.1 Genetic optimism	Portrays psychiatric genetics as having perceived positive impact on society.
6.2 Genetic pessimism	Portrays psychiatric genetics as having perceived negative impact on society.
6.3 Clinical promises (in years)	Makes predictions about future availability of relevant genes, genetic tests or treatments.
6.4 May never happen	Makes predictions that relevant genes may never be found or that genetic tests or molecular-based treatment may never be developed.

CODE	DESCRIPTION
7. Perceived clinical utility (6 codes)	**How does journalist portray clinical outcomes of psychiatric genetics?**
7.1 Genetic susceptibility testing	Mentions scope for development of genetic tests.
7.2 Preventive or early intervention	Mentions scope for presymptomatic preventive intervention(s) based on genetic profile.
7.3 More effective diagnosis or treatment	Implies genetic information will aid diagnosis and treatment.
7.4 Pharmacogenetics	Mentions potential for medication to be tailored to genetic profile.
7.5 Personalised medicine	Mentions potential for psychiatric treatment in general to be tailored to genetic profile.
7.6 Gene therapy	Mentions therapeutic outcome that involves manipulation of relevant genes.
8 Ethical and social issues (7 codes)	**How does journalist portray ethical and social issues of psychiatric genetics?**
8.1 Genetic discrimination	Mentions potential for discrimination against those with a genetic risk profile e.g. in areas of insurance, employment, health care, education, socially.
8.2 Privacy	Mentions issues about privacy or confidentiality regarding personal genetic information.
8.3 Eugenics	Mentions ethical issues arising from the possibility of eugenics.
8.4 Access	Mentions potential inequitable access to future psychiatric genetic services.
8.5 Right to know/ to not know	Mentions rights of patient and/or relatives to be informed or not informed of genetic risk after genetic testing.

CODE	DESCRIPTION
8 Ethical and Social Issues	
8.6 Impact on relatives	Mentions issues for asymptomatic relatives.
8.7 Increased risk of adversity	Mentions risk of despair/suicide as a result of being identified with increased genetic risk.
9 Stigma (2 codes)	**How does journalist portray impact of psychiatric genetics on stigma?**
9.1 Stigma increases	Implies genetic information about the disorder(s) may lead to e.g. negative labelling, negative attitude or social distancing.
9.2 Stigma decreases	Implies genetic information about the disorder(s) may facilitate e.g. medical legitimisation, shift of responsibility from self to biology, or may alleviate guilt.

Papers Published in Peer-Reviewed Journals

P.1   Wilde et al. (2009) Community attitudes towards mental health interventions for healthy people on the basis of genetic susceptibility *Aust N Z J Psychiatry* 43:11, 1070-1076

P.2   Wilde et al. (2010) Public interest in predictive genetic testing, including direct-to-consumer testing, for susceptibility to major depression: preliminary findings *Eur J Human Genet* 18, 47-51

P.3 - Wilde et al (In press) Community interest in predictive genetic testing for susceptibility to major depressive disorder in a large national sample. *Psychol Med*

P.1 - WILDE ET AL (2009) COMMUNITY ATTITUDES TOWARDS MENTAL HEALTH INTERVENTIONS FOR HEALTHY PEOPLE ON THE BASIS OF GENETIC SUSCEPTIBILITY *AUST NZ J PSYCHIATRY* 43:11, 1070-1076

Community attitudes towards mental health interventions for healthy people on the basis of genetic susceptibility

Alex Wilde [a]; Bettina Meiser [b]; Philip B. Mitchell [c]; Peter R. Schofield [d]

[a] Black Dog Institute, Sydney, New South Wales, Australia [b] Prince of Wales Clinical School, University of New South Wales, Sydney, New South Wales, Australia [c] School of Psychiatry, University of New South Wales, Black Dog Institute, Sydney, New South Wales, Australia; Brain Sciences UNSW,, Sydney, New South Wales, Australia [d] Prince of Wales Medical Research Institute, Sydney, New South Wales, Australia; School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia; Brain Sciences UNSW, Sydney, New South Wales, Australia

Online Publication Date: 01 November 2009

PLEASE SCROLL DOWN FOR ARTICLE

Community attitudes towards mental health interventions for healthy people on the basis of genetic susceptibility

Alex Wilde, Bettina Meiser, Philip B. Mitchell, Peter R. Schofield

Objectives: The aim of the present study was to evaluate, using serotonin transporter genotyping as an example, the preparedness of individuals from an urban general population identified with hypothetical genetic risk for a depressive disorder to moderate risk through cognitive or behavioural intervention. It also evaluated endorsement of genetic and environmental causal attributions of mental illness.

Method: A qualitative approach using focus group methodology was selected as most appropriate because these issues are relatively unexplored. Participants (n = 36) aged ≥18 years from metropolitan Sydney discussed their understanding of the role of genetic and environmental risk factors in mental illness and attitudes towards pre-symptomatic interventions based on genetic risk information.

Results: Thirty-six participants attended four focus groups involving 8–10 participants per group. Participants predominantly viewed genetic risk factors for depression as predisposing rather than causal, with environmental risk factors acting as triggers. Hypothetical identification with a genetic variant suggesting predisposition to depression prompted strong interest in seeking further information about predictive genetic testing from medical professionals, willingness to reduce life stress, drugs and alcohol intake, willingness to increase exercise, and willingness to undertake cognitive and behavioural interventions at a pre-symptomatic stage. Mixed views prevailed as to whether stress was a modifiable risk factor. Preventive intervention at a presymptomatic stage of depression was viewed negatively in a minority of participants due to a fatalistic attitude towards a genetic predisposition and attitudes that intervention was futile in the absence of symptoms.

Conclusions: There is a likely public demand for preventive mental health interventions for healthy people on the basis of genetic susceptibility if predictive genetic testing becomes available in psychiatry. The findings have implications for general practitioner and public education about predictive genetic testing for susceptibility to common multifactorial disorders for at-risk groups.

Key words: health behaviour, major depression, predictive genetic testing.

Alex Wilde, PhD candidate (Correspondence)

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Bettina Meiser, Associate Professor

Prince of Wales Clinical School, University of New South Wales, Sydney, New South Wales, Australia

Philip B. Mitchell, Scientia Professor

School of Psychiatry, University of New South Wales, Sydney, New South Wales, Australia; Black Dog Institute, Sydney, New South Wales, Australia; Brain Sciences UNSW, Sydney, New South Wales, Australia

Peter R Schofield, Professor

Prince of Wales Medical Research Institute, Sydney, New South Wales, Australia; School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia; Brain Sciences UNSW, Sydney, New South Wales, Australia

Received 6 April 2009; accepted 15 May 2009.

Rapid advances in genetic research over the past decade have led to identification of a substantial number of candidate genes associated with susceptibility to common complex disorders of public health significance including coronary artery disease, breast cancer, type 2 diabetes and major depression [1].

Identification of groups with an increased genetic risk for such disorders presents an opportunity to target interventions that modify specific environmental risk factors at a pre-symptomatic stage, with the potential to significantly reduce burden of disease. Clinical utility, acceptability and potential health impact of pre-symptomatic genetic testing as a preventive intervention is currently the subject of contentious debate, but few data exist to guide policy and ethical decision-making [2]. Given current concerns about the rapid expansion of commercial predictive genetic tests for multifactorial diseases marketed direct to consumer (DTC), research about how the public might use genetic risk information to change health behaviour is needed.

Around 50 predictive genetic tests purported to indicate risk for a wide range of common multifactorial diseases are currently marketed DTC via the Internet. Although some of these tests are available in clinical practice, many are based on a small number of unreplicated studies with uncertain clinical validity [3].

In psychiatry, a psychiatric gene–disease association that has been widely replicated by a large number of studies thus far is an interaction between a functional polymorphism in the promoter region (5-HTTLPR) of the serotonin transporter gene (SCL6A4) and exposure to stressful life events in increasing the likelihood of depression in non-clinical populations of adults [4–7], adolescents [8] and children [9]. The evidence suggests that homozygosity for the short allele (s/s) of the serotonin transporter gene-promoter region is associated with depression on exposure to multiple stressful life events [4–9]. The s/s variant is thought to play a role in mediating response to stress, with s/s individuals demonstrating hyperreactivity to stressors and/or deficient problem-solving coping, which may convey increased risk to future depression [10].

Since the completion of the present study a recent meta-analysis found no evidence for a 5-HTTLPR by environment interaction in association with an increased risk of depression [11]. However, 5-HTTLPR genotyping remains a good hypothetical example by which to evaluate attitudes to preventive interventions based on genetic testing for a risk of a common complex disorder.

Effective mental health intervention, based on genetic susceptibility, will depend upon community attitudes towards behavioural change to reduce risk, and understanding of uncertain penetrance, relationship between genes and environment, and potential to modify environmental risk factors.

Recent debate highlights popular attitudes about the right to know one's own genetic information [12], and that predictive genetic tests, especially those available DTC, offer autonomy and empowerment for the individual [13]. Critics question whether it is responsible to offer genetic tests if their predictive value is low, and if there is no associated treatment available [14]. Implications cited include a potential for a low-risk result to provide false reassurance, or a high-risk result to cause fatalistic thinking based on a belief that a genetic component for a disorder makes the disorder less preventable [15,16]. Both circumstances could demotivate an individual to engage in mental health interventions [14].

Previous studies evaluating potential to change health behaviours in association with genetic risk information have focused on breast cancer [17], heart disease [15], smoking [18], familial hypercholesterolemia [15,19], and Alzheimer's disease [20], but not psychiatric disease. It is generally thought that intention to change behaviour is a poor indicator of uptake of an intervention [21]. Fatalistic attitudes towards genetic risk for common complex disorders have been more commonly observed in general populations rather than among individuals informed of a genetic predisposition [19]. Empirical evidence suggests that provision of genetic risk information to the individual may prompt uptake of new health behaviours [17–19].

Only anecdotal evidence is available about how genetic risk information involving psychiatric disorders might be interpreted and used by patients [22]. Because serotonin transporter genotype-major depression associations are replicated and 5-HTTLPR genotyping has been commercially available DTC in the USA, we use this genetic test as an example to qualitatively evaluate among the general population, preparedness to modify risk at a pre-symptomatic stage through preventative behaviour based on a hypothetical genetic susceptibility to major depression.

Methods

The present results were obtained as part of a broader qualitative study, which also explored interest in genetic testing [23] and perceived impact of media portrayal of genetics and mental illness. The results regarding the latter topics will be reported separately.

Because this is a relatively unexplored area of enquiry, a qualitative methodology was used. There has been an upsurge in interest in studies that examine attitudes, beliefs and experiences of people in connection to health-care

issues, and qualitative methodology has been increasingly recognised in evidence-based clinical research [24].

Participants

A market research company was engaged to randomly recruit 10 participants each to four or more focus groups from their database of 10 000 members of the public, ensuring an even mix of gender, age and sociodemographic backgrounds. Eligibility criteria included being ≥18 years, fluent in English, resident in the Sydney metropolitan area and not having participated in any research in the previous 6 months. Ethical approval for the study was provided by the relevant Institutional Review Board (Human Research Ethics Committee, University of New South Wales, Australia).

Focus group interviews

Participants completed a short questionnaire that included items about age, sex, and highest education level. Participants were asked to indicate whether they had prior knowledge or experience of the subject of mental illness. They were not obliged to disclose personal or family history of mental illness.

The focus groups were conducted in accordance with widely accepted standards of focus group methodology [25]. In particular, at the beginning of each focus group the participants were assured of confidentiality, the discussions were videotaped and the facilitator periodically summarised discussions to check correct understanding.

The focus groups were facilitated by the first author (a health research scientist and medical journalist) and observed by the second author (a research psychologist). The observer also took written notes of the main themes discussed. An interview guide was developed on the basis of a review of the relevant literature with input from all authors. The analysis of the focus group interviews involved the use of verbatim transcripts.

Genotyping for the *5-HTTLPR* polymorphism was framed to participants as a 'genetic test to determine whether an individual has an increased risk for developing depression in the event of experiencing significant adversity'. A genetic test result that was positive for the short-short (s/s) variant of the *5-HTTLPR* polymorphism was framed to participants as indicating an 'increased risk for depression'.

Analysis

The conceptual approaches of Patton, and Miles and Huberman were used to guide the analysis [26,27]. A detailed coding scheme was developed and transcripts were coded by the first author. This involved coding each unit of meaning and comparing these with recurring patterns and discrete categories. A conceptually clustered coding tree was prepared to facilitate analysis both within and across themes.

Ten per cent of the transcripts were recoded by the second author, to identify any discrepancies in interpretation of codes and refine the coding scheme. Discrepancies were resolved by discussion and consensus. Coded transcripts were subsequently analysed for emergent themes arising from the transcripts [26,27]. Data analyses were iterative and the results from each focus group were used to suggest additional lines of questioning in subsequent focus groups to ensure that divergent points of view could be expressed.

The qualitative data analysis computer program QSR N6 (NUD*IST6; QSR International, Melbourne, Vic, Australia) was used to facilitate comparisons between affected and unaffected participants as well as other aspects of the analysis.

Corresponding to the qualitative nature of the data, focus group discussions were designed to identify the range of beliefs rather than extent to which participants held particular beliefs. Immediately prior to discussing attitudes towards mental health interventions based on a hypothetical personal genetic risk for depression, participants had discussed perceived implications of predictive genetic testing and beliefs about the causes of mental illness.

Results

Participation and demographics

Thirty-six (18 female, 18 male) of 40 invitees were recruited to a total of four focus groups held in four locations across Sydney. Recruitment was discontinued after the fourth focus group, when informational redundancy was achieved, in accordance with widely accepted standards of qualitative methodology [27].

During focus group discussions, 14 participants spontaneously disclosed a personal or family history of depression, bipolar disorder or schizophrenia. Hereafter, participants reporting a personal or family history of depression are referred to as 'affected', while those who did not are referred to as 'unaffected'. Citations referring to affected participants are denoted with [A] and those referring to unaffected participants with [U]. Demographic characteristics of unaffected and affected participants are shown in Table 1. The mean age was 41 years (range = 20–65 years).

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Table 1.   *Subject characteristics*

Variable	Affected [A] (n = 14)	Unaffected [U]† (n = 22)	Total sample† (n = 36)
Sex	n	n	n
Male	5	13	18
Female	9	9	18
Age (years)†			
18–29	2	5	7
30–39	6	6	12
40–49	1	3	4
50–59	4	2	6
60–69	1	5	6
Highest education level completed†			
Tertiary	9	9	18
High school	5	12	17

†Missing value due to participant declining to answer age and education level questions.

Anticipated health behaviours on receiving s/s genotype result

The majority of participants (11 affected, 20 unaffected) thought that being identified with an increased genetic risk of major depression would have a personal impact. Participants anticipated that they would increase vigilance for symptoms, seek information about depression, make lifestyle changes, undertake preventative strategies or do nothing.

Increased vigilance

The majority of affected participants and approximately half of the unaffected participants agreed that receiving a genetic test result indicating an increased risk for depression would encourage them to be vigilant for signs and symptoms of the disorder. Several affected participants thought vigilance would make them more likely to act on warning signs for depression and seek medical help as appropriate: 'So if the symptoms and signs are showing up... you're aware so you're more likely to notice them.' [A].

One participant observed that public education about the familial aspect of depression would be an important intervention to enable family members to be vigilant for symptoms in each other [U]; while another remarked that this strategy could be life-saving [U].

Prompt information seeking

Many participants said that an increased risk result would prompt them to seek information about depression, its symptoms and the meaning of being at increased genetic risk. One said: 'I'd want to get a better educated

person ... just understand what the implications may or may not be ....' [U].

Many participants showed trust in being advised by their doctors: 'But if I did have that sort of thing I would go and see the doctor and do something because I wouldn't like to be caught out.' [U].

One unaffected participant said she would 'go down the natural path' rather than see a general practitioner (GP) [U]. Another pointed out that people with an increased genetic risk should also be made aware of treatment options for depression and be advised on how to access medical services [U].

One participant, despite suggesting he would seek further information if he received an increased risk result, had a fatalistic view that could negatively impact on effectiveness of genetic counselling and behavioural intervention: 'It's a done deal isn't it? You've got your DNA, you've got your genetics and you're in no position to alter them' [U].

Prompt lifestyle changes

Participants who said they would make lifestyle changes if genotyping identified an increased risk for depression considered the potential to modify environmental risk factors including stress, diet, exercise and drug and alcohol intake. Several participants were in favour of minimising stress as an intervention: 'You'd have to try and get as many stresses out of your life as possible...if you've got a stressful job, get rid of the job' [U].

Other participants, while agreeing that drugs and alcohol intake were modifiable risk factors, were cautious about whether stress could be modified or avoided: '... you can cut down ... the drugs and alcohol and stress you can try but you're not going to erase that from

your lifestyle' [U]. 'Yeah, .. marijuana and drugs and alcohol...definitely something to be avoided if you've got a disposition but you can't avoid stress throughout life, you just can't' [A].

One participant said a genetic test result indicating an increased risk for depression would encourage him to maintain a healthy lifestyle [U]; while another remarked that she would adjust her diet and take more exercise as well as 'seek some sort of help so as you can be steered in the right direction' [A]. Two participants observed that individual differences in response to stress would impact on attempts to implement preventive strategies [A] [U].

Prompt preventative behaviour

One participant, who disclosed a history of depression, commented that predictive genetic testing, had it been available to her prior to her diagnosis, would have enabled her to learn coping strategies in advance so that her depression 'could possibly have been minimalised or prevented' [A]: 'I would have liked to have known [in advance] because the things I've learnt how to cope with it over time like panic attacks...how to breathe properly...I think maybe I could have implemented some of those tools earlier. It might have stopped me from getting really sick when I did' [A].

Another participant said that if she received an increased risk result she would start a course of antidepressants as a preventive strategy [A]. Two participants agreed that preventative medication could be used as a preventative measure while observing that there could be potential for harm [U] [U]; while two were against such a strategy [A] [A].

Doing nothing

Two of the four unaffected participants who said that they would do nothing if they received a predictive genetic test result that showed an increased risk for depression expressed the views: '...why treat something if you don't have it?' and '... why educate yourself on something and worry yourself when it's probably not going to happen.'

Causal attributions for mental illness

The study found support for a genetic model for major depression with genetic factors viewed as predisposing rather than causal. Some participants perceived depression as less severe, less enduring and more likely to be attributed to stress rather than genetic factors than other psychiatric disorders including bipolar disorder and schizophrenia. Two participants observed that individual differences in response to stress would impact on attempts at preventive strategies.

Both affected and unaffected participants suggested that possible environmental factors that could trigger a mental illness were 'alcohol, drugs, stress, chemical imbalance, poverty, general trauma, emotional disturbance, relationship breakdown, family environment, isolation, trauma in childhood, social environment, disadvantage' and 'arguments all the time'.

Discussion

The present study supports previous findings that positive attitudes towards a range of mental health intervention strategies at a pre-symptomatic stage exist [28]. These include interest in information and genetic counselling from GPs about the implications of having an s/s genotype, about depression and its risk factors and symptoms, and about future options for treatment and management. There was minor support for preventive medication among affected individuals as a pre-symptomatic intervention.

Although some participants were ambivalent about whether stress could be modified, positive attitudes were reported towards willingness to engage in lifestyle interventions such as reducing stress, drugs and alcohol intake and increasing exercise. The results suggest that mental health interventions that facilitate learning of effective coping skills are likely to be well-received as preventive strategies for target groups at a pre-symptomatic stage.

A number of findings have the potential to moderate uptake of future preventative mental health strategies among individuals identified as having the s/s variant of the 5-HTT promoter polymorphism. These include fatalistic attitudes that one's DNA is immutable, thus rendering environmental modification useless, perceptions of pointlessness of interventions in the absence of symptoms, and mixed or confused views on causal attributions for major depression.

Finding community endorsement of a contribution of both genetic and environmental factors in the development of mental illness and perceptions that genetic predispositions can be modified by adjusting environmental risk factors supports previous studies [29–31]. These endorsements suggest that target groups might be receptive to preventive programmes that involve predictive genetic testing associated with preventive cognitive and behavioural interventions that modify environmental risk factors. This is especially true in the light of greater endorsement of environmental risk factors as a cause for major depression than other psychiatric disorders.

Because provision of information about individual genetic risk alone may not be sufficient to change health-related behaviour [12,13,32], it will be necessary to evaluate the synergistic effects of individual genotype with personal and family history of psychiatric disorders, and lifestyle and environmental factors that regulate gene expression [5,22].

Ethical issues surrounding the use of predictive genetic testing in psychiatry, such as risk of discrimination and loss of privacy, require further investigation. Effective mental health interventions and appropriate genetic counselling should be established before *5-HTTLPR* genotyping is offered in clinical practice.

Limitations of the study should be mentioned. Some participants may have interpreted the term 'significant adversity', or stressful life events, to mean everyday life stress, which could have affected anticipated health behaviour based on perception of modifiable nature of risk factors. Intention to change health behaviours in response to genetic risk information shown in the present study may not reflect actual change. Although every effort was made to include all participants throughout the focus group discussion, there may be a bias towards the views of a dominant minority. Reporting of a personal or family history of mental illness was voluntary, which may have resulted in the affected group being represented only by those willing to disclose such information.

This qualitative study has identified only the range of attitudes towards anticipated health behaviours based on genetic risk information, and not the extent to which they are held. These qualitative findings now require quantitative replication using a survey design in large representative non-clinical general population samples before recommendations about mental health interventions based on genetic risk can be made on a broader scale.

Acknowledgements

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P.2 - WILDE ET AL (2010) PUBLIC INTEREST IN PREDICTIVE GENETIC TESTING, INCLUDING DIRECT-TO-CONSUMER TESTING, FOR SUSCEPTIBILITY TO MAJOR DEPRESSION: PRELIMINARY FINDINGS

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ARTICLE

Public interest in predictive genetic testing, including direct-to-consumer testing, for susceptibility to major depression: preliminary findings

Alex Wilde*,1,3, Bettina Meiser2, Philip B Mitchell1,3,6 and Peter R Schofield4,5,6

The past decade has seen rapid advances in the identification of associations between candidate genes and a range of common multifactorial disorders. This paper evaluates public attitudes towards the complexity of genetic risk prediction in psychiatry involving susceptibility genes, uncertain penetrance and gene–environment interactions on which successful molecular-based mental health interventions will depend. A qualitative approach was taken to enable the exploration of the views of the public. Four structured focus groups were conducted with a total of 36 participants. The majority of participants indicated interest in having a genetic test for susceptibility to major depression, if it was available. Having a family history of mental illness was cited as a major reason. After discussion of perceived positive and negative implications of predictive genetic testing, nine of 24 participants initially interested in having such a test changed their mind. Fear of genetic discrimination and privacy issues predominantly influenced change of attitude. All participants still interested in having a predictive genetic test for risk for depression reported they would only do so through trusted medical professionals. Participants were unanimously against direct-to-consumer genetic testing marketed through the Internet, although some would consider it if there was suitable protection against discrimination. The study highlights the importance of general practitioner and public education about psychiatric genetics, and the availability of appropriate treatment and support services prior to implementation of future predictive genetic testing services.
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INTRODUCTION

The identification of candidate genes thought to confer susceptibility to psychiatric illness, manifesting on exposure to stressful life events, presents an opportunity to predict high-risk groups and reduce the burden of psychiatric disease through intervention strategies at a pre-symptomatic stage. Risk prediction and preventative interventions, based on first episode psychosis, are already in place for youth at high risk for schizophrenia and other psychotic disorders. Studies show that early interventions in this group, such as pharmacotherapy and psychotherapy, may delay or even prevent progression to a diagnosable psychotic disorder such as schizophrenia. Predictive genetic testing for markers of mental illness has thus far not been studied in prospective early intervention studies.[1] Effective interventions that use genetic and environmental risk information will depend on public understanding of the complexity of interactions between susceptibility genes of uncertain penetrance and environmental risk factors. The recent proliferation of commercial start-up genetic testing companies marketing predictive genetic tests directly to the public has raised concerns about predictive validity and potential health impact of such tests.[2] Consumers may be at risk of selecting inappropriate tests, misinterpreting results and making harmful health decisions.[3] Private

biotechnology laboratories, based predominantly in USA, UK and Iceland, are currently marketing more than 50 predictive genetic tests direct-to-consumer (DTC) through the Internet. Some of these tests are available for use in clinical practice, but for some, including the susceptibility tests for psychiatric disorders, there are few published data thus far to support clinical validity.[4]

A gene–disease susceptibility association that has been replicated by a large number of studies is an interaction between a functional polymorphism in the promoter region (5-HTTLPR) of the serotonin transporter gene (SCL6A4) and exposure to stressful life events in increasing the likelihood of a major depression in non-clinical populations of adults,[5–8] adolescents[9] and children.[10] The evidence suggests that individuals homozygous for the short allele (s/s) of the serotonin transporter gene-linked polymorphic region may be at an increased risk for depression on exposure to multiple stressful life events.[5–10] Since the completion of this study, a recent meta-analysis has found no evidence for a 5-HTTLPR by environment interaction in association with an increased risk of depression,[11] however, 5-HTTLPR genotyping remains a good hypothetical example by which to evaluate attitudes to predictive genetic testing for a risk for a common complex disorder.

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Psychosocial issues associated with predictive genetic testing for susceptibility to major depression are likely to be more complex than for Mendelian monogenic disorders because test results are not definitive. There will be implications for public policy and ethics with an impact on stigma[12–15] and concerns about potential misuse of genetic risk information, for example, through employment and insurance discrimination.[16]

Government genetics advisory bodies around the world have commenced expert consultations and public meetings to determine how predictive genetic testing should be regulated,[3,17,18] however, there is a dearth of scientific research to inform national and international policy.

Previous international scientific research in this area is predominantly limited to preliminary and/or qualitative studies on attitudes towards genetic risk information and genetic testing among members of families who have multiple relatives affected by bipolar disorder or schizophrenia.[12,19–22] These studies have generally found positive attitudes towards predictive genetic testing, and a recent quantitative study involving families with a high density of bipolar disorder showed that interest in testing increased with the certainty indicated by the test.[23] As no research to date has evaluated attitudes among the general population towards predictive genetic testing for depression risk and beliefs about the psychosocial implications, this study aimed to qualitatively assess public understanding of, and attitudes towards, risk prediction involving susceptibility genes for depression based on 5–HTTLPR genotyping.

MATERIALS AND METHODS

The results reported here were undertaken as part of a broader qualitative study, which also explored attitudes towards preventative mental health interventions based on genetic risk,[24] as well as the perceived impact of media portrayal of genetics and mental illness. These findings will be reported separately.

As this is a relatively unexplored area of enquiry, a qualitative methodology was used. There has been an upsurge in interest in studies that examine attitudes, beliefs and experiences of people in connection to health care issues, and qualitative methodology has been increasingly recognised by evidence-based clinical researchers.[25]

Participants

A market research company was engaged to randomly recruit 10 participants each to four or more focus groups from their database of 10 000 members of the public unselected for disease risk, ensuring an even mix of gender, age and socio-demographic backgrounds. Eligibility criteria included being 18 years or older, fluent in English, residing in the Sydney metropolitan area and should not have participated in any research in the previous six months. Ethical approval for the study was provided by the relevant Institutional Review Board (Human Research Ethics Committee, University of New South Wales, Australia).

Focus group interviews

Participants were naïve to the focus group topic. They completed a short questionnaire that included items about age, sex, language spoken at home, occupation and highest education level completed. Participants were asked to introduce themselves and indicate whether they had prior knowledge or experience of the subject of mental illness. They were not required to disclose personal or family history of mental illness.

The focus groups were formed in accordance with widely accepted standards of focus group methodology.[26] They were facilitated by the first author (a research scientist and medical journalist) and observed by the second author (a research psychologist). Focus groups were recorded on digital video and the observer took written notes of the main themes discussed.

An interview guide was developed on the basis of a review of the relevant literature with input from all authors exploring the following topics: (i) interest in predictive genetic testing (genotyping for the 5–HTT promoter polymorphism) to determine susceptibility to major depression and (ii) attitudes towards potential for social stigma, discrimination and issues of DNA privacy.

Genotyping for the 5–HTT promoter polymorphism was framed to participants as a 'genetic test to determine whether an individual has an increased risk for developing depression in the event of experiencing significant adversity'. A test result showing the s/s (higher risk) genotype of the 5–HTT promoter polymorphism was framed to participants as a genetic result indicating an 'increased risk for depression'.

Analysis

The conceptual approaches of Patton,[27] and Miles and Huberman[28] were used as guides for the analysis. A detailed coding scheme was developed and transcripts were coded by the first author. Ten percent of the transcripts were recoded by the second author, to identify any discrepancies in the interpretation of codes and refine the coding scheme. Discrepancies were discussed between coders to provide opportunities for developing further coding and consensus.[25]

Coded transcripts were subsequently analysed for emergent themes with the assistance of the software package QSR N6 (Qualitative Solutions and Research, Doncaster, Victoria, Australia), which facilitated comparisons between affected and unaffected participants as well as other aspects of the analysis.[28]

Corresponding to the qualitative nature of the data, focus group discussions were designed to identify the range of beliefs rather than extent to which participants held particular beliefs. However, to provide an indication of the extent of interest in predictive genetic testing for susceptibility to depression, every participant was asked whether they would undergo genotyping for the 5–HTT promoter polymorphism if it was available, and why, before and after discussion of perceived positive and negative psychosocial implications.

As the aim of the study was to evaluate attitudes towards predictive genetic testing among individuals for whom such testing would carry greater hereditary implications compared with those without a personal or family history, participant quotations were coded according to lived experience (personal and familial implications) of mental illness: eg [A] (affected): reported personal or family history of major depression, bipolar disorder or schizophrenia; or [U] (unaffected): no reported personal or family history of major depression, bipolar disorder or schizophrenia. Interest in genetic testing was also coded: [YY], interested in having a genetic test for susceptibility to major depression both before and after considering implications; [YN], initially interested in having the genetic test but not after considering implications; [NN], not interested in having the genetic test both before and after considering implications. Although an NY code was a theoretical possibility, it was not used because no participants fell into this category.

RESULTS

Participation and demographics

Thirty-six people (18 female, 18 male) participated in four focus groups (8–10 people per group) held at four locations across Sydney. Recruitment was discontinued after informational redundancy was achieved in the fourth focus group, in accordance with standard qualitative methodology.[28] During focus group discussions, 14 participants spontaneously revealed a personal or family history of major depression, bipolar disorder or schizophrenia. Demographic characteristics of affected and unaffected participants are shown in Table 1. The mean age was 41 (range 20–65 years).

Interest in predictive genetic testing for 5–HTTLPR genotype

At the beginning of the discussion, the majority of participants (10 affected, 14 unaffected) indicated an interest in undergoing a genetic test for susceptibility to major depression, if the test was available. Unaffected participants who said they would be interested in having predictive testing were more hesitant and tended to attach conditions. Table 2 shows interest in undergoing 5–HTTLPR genotyping before and after discussion of perceived positive and negative implications,

Table 1 Demographic characteristics of the sample

Variable	Affected (A)[a] (N=14) N	Unaffected (U)[b] (N=22) N	Total sample[c] (N=36) N
Sex			
Male	5	13	18
Female	9	9	18
Age (years)[c]			
18–29	2	5	7
30–39	6	6	12
40–49	1	3	4
50–59	4	2	6
60–69	1	5	6
Highest education level completed[c]			
Tertiary	9	9	18
High school	5	12	17

[a]Self-reported personal or family history of major depression, bipolar disorder or schizophrenia.
[b]No reported personal or family history of major depression, bipolar disorder or schizophrenia.
[c]Missing value – participant declined questions related to age and education.

Table 2 Interest in predictive genetic testing for *5-HTTLPR* genotype

Interest	Participants		
	Affected	Unaffected (unsure)[a]	Total (unsure)[a]
Initially interested	10	14 (2)	24 (2)
No longer interested after discussion	4	5	9
Still interested after discussion	6	7 (4)	13 (4)

[a]Participants who were unsure of whether they would undergo such a test.

and reading several media articles about various aspects of genes and mental illness. Participants who were initially interested in having *5–HTTLPR* genotyping but who changed their mind after the discussion, cited fear of genetic discrimination and loss of privacy as major reasons. No participants changed their mind in the opposite direction.

Perceived benefits of predictive testing for *5–HTTLPR* genotype

Benefits for families. Both affected and unaffected participants thought predictive testing for susceptibility to depression would be of greater benefit to those with a family history of the disorder.

'I couldn't imagine having the test unless there was somebody in the family with mental illness' [A/YY].

Scope for early intervention. Both affected and unaffected participants thought *5–HTTLPR* genotyping would help them be ready to seek early help. One remarked: '…forewarned is forearmed,' which he believed would enable him to '…deal with it should it arise' [U/YY].

Another said:

'…I've seen my mum live through it, I think it's so much better to know straight out, start as soon as you can with whatever help you can get.' [A/YY].

One participant suggested *5–HTTLPR* genotyping could be a useful part of a general health check-up [A/YY]. One participant said knowledge of one's genetic risk could help people put techniques in place that might minimise or prevent the development or severity of depression. [A/YN].

Reduce social stigma. Several affected participants thought evidence of a genetic component would help validate depression and other mental illnesses as physical illnesses, which might decrease social stigma. One suggested this would lead to improved government funding for mental health research. Another disagreed with predictive genetic testing for susceptibility to depression because 'the test is not definitive', and 'no prevention is available.'

Conditions attached to interest in predictive genetic testing. Conditions set by unaffected participants interested in having *5–HTTLPR* genotyping included: 'if it ran in the family;' [U/NN], 'if I needed it,' [U/YY], 'if the doctor referred me,' [U/YY]. One participant saw little point in having a predictive genetic test without availability of related interventions:

'You'd just wait for the signs of symptoms to come. Nothing is going to change; you don't start taking something just because there's a possibility you might [develop depression].' [U/NN].

Perceived disadvantages of predictive genetic testing for *5–HTTLPR* genotype

Fear of loss of privacy. Although most participants said they trusted a genetic test result would remain private and confidential if obtained through the public health system, some participants were worried that privacy could not be guaranteed. One participant cited this as the reason why she would not undergo *5–HTTLPR* genotyping:

'…if [the test result] fell into the wrong hands or …you know we just live in such a fish bowl these days and no, couldn't bear the thought of it.' [U/NN].

Risk of discrimination. Many participants were concerned that undergoing *5–HTTLPR* genotyping could lead to discrimination by insurance companies and employers; which influenced several unaffected participants against undergoing a predictive test, and caused another to change her mind:

'I know that if I had a test well it probably would come back positive. And if found that out and I couldn't get insurance well then I'd say no to a test.' [A/YN].

Risk of fatalistic thinking. Both affected and unaffected participants thought they might develop fatalistic thinking if they were found to have the *5–HTTLPR* s/s variant:

'…once you find out…that you are in this predisposition it might send you over the mark …you'd be worrying the whole time – that's going to cause it.' [A/YN].

One participant viewed having the s/s variant as definitive with negative consequences:

'I mean you might be okay and then it comes back that you're depressed or you've got bipolar [disorder] and then you go and neck yourself.' [U/YN].

One participant disagreed with the fatalistic view, and emphasised the importance of awareness:

'I'd be worried if I wasn't aware…if it's 80% risk or something like that at least I know, I'm aware that this could happen. I'm not going to treat it as if it is happening.' [A/YY].

Increase social stigma. Several affected and unaffected participants anticipated that predictive testing for predisposition to depression would not reduce social stigma attached to the disorder but could increase it:

'Whilst I see that [predictive genetic testing] might be valuable to helping a person… I think social implications, social stigma is the major problem.' [A/YY].

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P.3 - WILDE ET AL (IN PRESS) COMMUNITY INTEREST IN PREDICTIVE GENETIC TESTING FOR SUSCEPTIBILITY TO MAJOR DEPRESSIVE DISORDER IN A LARGE NATIONAL SAMPLE. *PSYCHOL MED*

Community interest in predictive genetic testing for susceptibility to major depressive disorder in a large national sample

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Background. Despite international concern about unregulated predictive genetic testing, there are surprisingly few data on both the determinants of community interest in such testing and its psychosocial impact.

Method. A large population-based public survey with community-dwelling adults ($n = 1046$) ascertained through random digit dialling. Attitudes were assessed by structured interviews.

Results. The study found strong interest in predictive genetic testing for a reported susceptibility to depression. Once the benefits and disadvantages of such testing had been considered, there was significantly greater interest in seeking such a test through a doctor (63%) compared to direct-to-consumer (DTC; 40%) ($p < 0.001$). Personal history of mental illness [odds ratio (OR) 2.58, $p < 0.001$], self-estimation of being at higher than average risk for depression (OR 1.92, $p < 0.001$), belief that a genetic component would increase rather than decrease stigma (OR 1.62, $p < 0.001$), and endorsement of benefits of genetic testing (OR 3.47, $p < 0.001$) significantly predicted interest in having such a test.

Conclusions. Despite finding attitudes that genetic links to mental illness would increase rather than decrease stigma, we found strong community acceptance of depression risk genotyping, even though a predisposition to depression may only manifest upon exposure to stressful life events. Our results suggest that there will be a strong demand for predictive genetic testing.

Introduction

Identifying healthy individuals with genotypes that suggest increased risk of psychiatric illness provides an opportunity to reduce the burden of disease through environment-specific intervention at a pre-symptomatic stage. Heritability estimates of 33–48% provide evidence of a genetic component for major depressive disorder (McGuffin et al. 1996; Kendler & Prescott, 1999) whereas lifetime risk for unaffected individuals with a first-degree relative with major depressive disorder is estimated to be 10–25% (Hill & Sahhar, 2006). However, as a complex disorder, the contribution of any single gene to the causation of depression is likely to be small as additional genetic and environmental risk factors must be taken into account.

Disclosure of genotyping information about risk for major depressive disorder (Wilhelm et al. 2009) or Alzheimer's disease (Green et al. 2009) to asymptomatic adults has been shown to provide a benefit to individuals with 'low-risk' variants and to cause low to modest distress to those with an 'increased risk' variant. Although most genetic testing is currently available only through a health-care provider, an increasing range of tests are being offered direct-to-consumer (DTC; Hudson et al. 2007) without medical supervision, raising concerns about the psychosocial impact of risk disclosure. This has stimulated popular debate about the right-to-know or not to know one's own genetic information, and whether predictive genetic tests, especially those available DTC, provide

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useful information about one's health (Shetty, 2008). Many genetic tests offered DTC involve unreplicated gene–disease associations and have uncertain predictive value and clinical utility (Kraft & Hunter, 2009). Furthermore, without medical supervision, consumers may be at risk of making uninformed health decisions (Cameron *et al.* 2009).

Few data exist on both the determinants of community interest in such testing and its psychosocial impact. Given current international concern about unregulated predictive genetic testing, such data are required urgently to inform national and international policy development.

Previous studies on attitudes towards genetic testing for susceptibility alleles thought to be involved in some mental illnesses have been limited predominantly to preliminary and/or qualitative studies involving people with an unspecified psychiatric diagnosis (Laegsgaard & Mors, 2008), people with multiple relatives affected by bipolar disorder (Smith *et al.* 1996; Trippitelli *et al.* 1998; Jones *et al.* 2002; Meiser *et al.* 2005, 2008) or schizophrenia (Austin *et al.* 2006; DeLisi & Bertisch, 2006), and psychiatrists (Smith *et al.* 1996; Jones *et al.* 2002; DeLisi & Bertisch, 2006). These studies have generally found positive attitudes towards predictive genetic testing for predisposition to psychiatric disorders. One recent quantitative study involving families with a high density of bipolar disorder showed that interest in hypothetical genetic testing increased with the degree of certainty indicated by the test (Meiser *et al.* 2008). Further studies reported strong support for predictive genetic testing for predisposition to psychiatric disorders but were limited to people with a diagnosis of major depressive disorder, bipolar disorder, schizophrenia and/or anxiety disorders participating in psychiatric genetic studies (Illes *et al.* 2003; Laegsgaard *et al.* 2009). Our previous qualitative study found positive public interest in depression risk genotyping, which was negatively influenced by the potential for discrimination and loss of privacy (Wilde *et al.* 2010). Participants showed trust in obtaining such a test through the medical system but were wary of DTC genetic testing services.

The present investigation is the first national population study to examine this issue for genetic variations associated with mental health in general. This study uses the hypothetical example of serotonin transporter genotyping as it has been previously reported to convey a gene–environment risk for major depressive disorder (Caspi *et al.* 2003; Eley *et al.* 2004; Kaufman *et al.* 2004; Kendler *et al.* 2005; Taylor *et al.* 2006; Wilhelm *et al.* 2006).

The present study proposes the following hypotheses: interest in predictive testing for a depression-risk genotype will be (i) greater if available from a doctor rather than DTC on the internet; and will be positively associated with (ii) having a personal history of mental illness and (iii) lower perceived social stigma attached to mental illness.

Method

Participants across Australia were recruited by a contracted market research company in May 2008 using random digit dialling of a computer-generated list of landline telephone numbers that use prefixes based on the geographic coverage of the sample's area, with the aim of producing a nationally representative sample. Respondents were selected from each household using a Computer Assisted Telephone Interviewing (CATI)-generated algorithm. Only those aged $\geqslant 18$ years and fluent in English were eligible to participate. Only one individual per household could participate. The interviews were completed until a target sample size of at least 1000 was reached. Ethical approval for the study was provided by the relevant Institutional Review Board.

Measures

Demographic characteristics

Data on sex, age, highest level of education achieved, current marital status and country of birth were collected using specifically designed multiple-choice items.

Clinical and family history data

Data on self-estimation of risk of depression were collected in a three-part question early in the survey: 'Compared with the average person, would you say your risk of depression is higher than average; lower than average; the same as the average person?'

Self-reported data on personal history of mental illness and exposure to mental illness through close relatives or close friends were collected on completion of the survey. Participants were asked 'have you or has a close relative or friend ever been diagnosed with depression, bipolar disorder or schizophrenia?' These terms were defined to participants.

Causal attributions for mental illness

Causal attributions to assess the perceived importance of different factors in causing a mental illness were derived from Meiser *et al.* (2007). Participants responded to all items using a five-point Likert-type scale ranging from 1 'not at all important' to 5 'extremely important'. For statistical analysis, items were
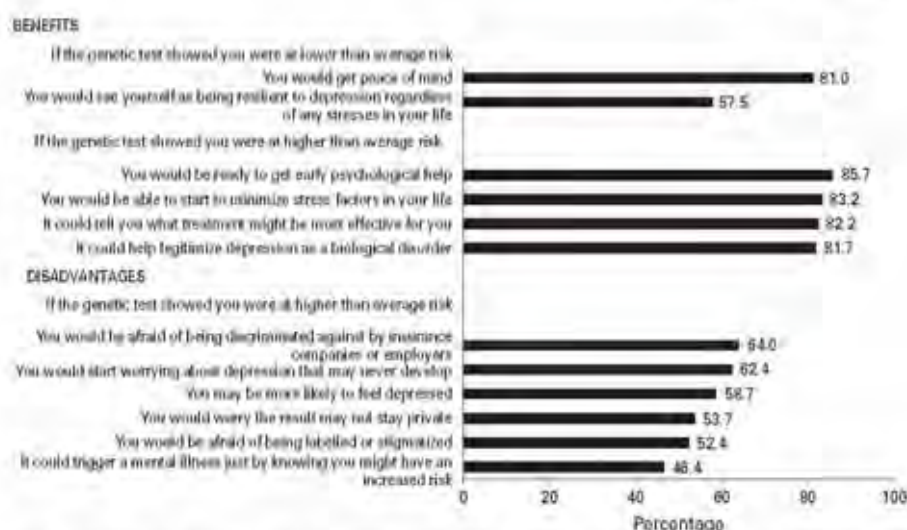
Fig. 1. Percentages of participants indicating agreement or strong agreement with a range of perceived benefits and disadvantages of depression-risk genotyping (maximum *n* = 1046).

grouped according to the exploratory factor analysis of Meiser *et al.* (2007), which yielded a four-factor solution with good internal consistency with item groupings representing (i) genetics, (ii) life stress, (iii) abuse and (iv) family environment.

Three items with five-point Likert-type response options were used to assess the degree of endorsement of perceptions about: gene–environment interactions as a causal mechanism (framed as 'mental illnesses are caused by an interplay of genetic risk and stressful life experiences'), incomplete penetrance as a mechanism of inheritance (framed as 'it is possible to have a genetic risk for a mental illness but never actually get the disorder') and no causal genetic factors (framed as 'it is possible to have a mental illness without a genetic risk').

Stigma

Perceptions about the impact of evidence for a genetic component for mental illness on stigma were explored using a three-point scale: 'stigma would decrease', 'a genetic basis for a mental illness would make no difference to stigma', and 'stigma would increase'.

Perceived benefits and disadvantages

Perceived benefits and disadvantages of predictive genetic testing were assessed using 12 items (see Fig. 1 for item wording) with five-point Likert-type response options ranging from 1 ('strongly disagree') to 5 ('strongly agree'). The measure is based on the results of our qualitative study, which explored the range of

perceived benefits and limitations of genetic testing for major depressive disorder (Wilde *et al.* 2010). These measures demonstrated good internal consistency in the present samples, with Cronbach's $\alpha = 0.65$ (benefits) and 0.76 (disadvantages). Summary scores were calculated for perceived benefits and disadvantages separately, with higher values indicating greater endorsement of perceived benefits or disadvantages.

Outcome variable: interest in having genetic testing for depression risk

Data on interest in predictive genetic testing were collected by (i) channel of access (i.e. through a doctor or DTC) and (ii) before and after participants were asked about perceived benefits and disadvantages of predictive testing. The latter two are reported as 'naïve interest' and 'considered interest' respectively. This produced four variables: naïve interest in having the test through a doctor; naïve interest in having the test DTC; considered interest in having the test through a doctor; and considered interest in having the test DTC. Interest in having depression risk testing was assessed by one item with four Likert-type response options ranging from 'no, definitely not', 'no, probably not', 'yes, probably', to 'yes, definitely' plus 'don't know'.

Questions were framed as: 'If a genetic test to determine your risk for developing depression in the event of experiencing stressful life events was available through (1) your own doctor, (2) via the internet

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directly to you from an overseas laboratory, would you be interested in having it?'

As the public health system is likely to be a future provider of predictive genetic testing to informed patients, 'considered interest in genetic testing through a doctor' was selected as the most appropriate outcome variable for the purposes of multivariate analyses. This variable was recoded into a binary variable by merging the 'definitely' and 'probably' options and redefining the new variable as 'yes, would consider' *versus* 'no, would not consider' genetic testing. 'Don't know' responses were not included in the new variable.

Statistical analyses

Data were explored initially with descriptive statistics. χ^2 cross-tabulations were analysed for naïve and considered interest through a doctor and through DTC channels. Bivariate associations between possible predictor variables and the outcome variable were first examined using an independent samples t test for continuous predictor variables, Mann–Whitney U tests for ordinal predictor variables and Pearson's χ^2 cross-tabulations for categorical predictors. All variables with a bivariate association with $p < 0.1$ were entered into a backward stepwise removal regression model until the only remaining variables were those with $p < 0.05$.

The following variables were assessed as possible predictor variables in the analysis of considered interest in depression-risk testing through accredited medical services: personal history of a mental illness, experience of a mental illness through a close relative or close friend, self-estimation of risk for major depressive disorder, causal attributions for mental illness, gene–environment interaction as a causal mechanism, incomplete penetrance as a hereditary mechanism, no causal genetic factors, perceived impact of a genetic component for mental illness on social stigma, and perceived benefits and disadvantages of having such a genetic test. All regression analyses were adjusted for age, sex, education level and country of birth.

Results

Participant characteristics

Of the 1544 eligible individuals contacted, 498 declined, resulting in 1046 completed surveys and a participation rate of 68%. Sociodemographic characteristics of the participants are presented in Table 1. Sixty-one per cent were female and 39% male compared to 50.2% and 49.8% respectively in the Australian adult resident population. The mean age of participants was 50.7 years [95% confidence interval

Table 1. *Summary of participant characteristics (maximum $n = 1046$)*

Sex	
Male	409 (39.1)
Female	637 (60.9)
Age [mean (s.d.) = 50.7 years (16.2), range 18–88]	
18–29	111 (10.6)
30–39	169 (16.2)
40–49	221 (21.1)
50–59	212 (20.3)
⩾60	330 (31.6)
Current marital status	
Married/*de facto*	661 (63.2)
Other	384 (36.8)
Country of birth	
Australia	815 (78.0)
Outside Australia (49 countries)	230 (22.0)
Highest level of education	
No post-school education	473 (45.4)
Post-school education	569 (54.6)
History of mental illness	
Personal[a]	
Yes	237 (22.7)
No	805 (77.3)
Close relative/friend[b]	
Yes	661 (63.7)
No	337 (36.3)
Self-estimation of risk for major depressive disorder[c]	
Higher than average	240 (23.2)
Lower than average	295 (28.5)
Same as average	500 (48.3)

s.d., Standard deviation.

Values are given as n (%).

[a] Refers to personal history of depression, bipolar disorder or schizophrenia.

[b] Refers to experience of depression, bipolar or schizophrenia through a close relative or close friend.

[c] Refers to personal estimation of risk for major depressive disorder compared to average population risk.

(CI) 49.7–51.7, range 18–88 years], compared to a mean of 47.0 years among the resident Australian population aged ⩾18 years. Twenty-two per cent (95% CI 22–25) were born overseas, compared to an estimated 25% of the resident population of Australia born overseas (Australian Bureau of Statistics, 2006).

Perceived benefits and disadvantages of predictive genetic testing for depression risk

Figure 1 details the proportions of participants who agreed or strongly agreed with a range of perceived benefits and disadvantages of genetic testing.

Table 2(a). *Items assessed for association with considered interest[a] in depression-risk genotyping (maximum n = 1046)*

	Interested in testing[a]			
Variable	n	%	χ^2	p
Sex				
Male	234	58.1		
Female	410	65.5	5.78	0.016[f]
Highest level of education				
No post-school education	309	66.6	5.68	0.017[f]
Post-school education	333	59.4		
History of mental illness				
Personal[b]				
Yes	189	81.8	46.4	<0.001[f]
No	455	57.3		
Close relative/friend[c]				
Yes	402	62.0		
No	239	64.1	0.42	0.52
Self-estimation of risk for major depressive disorder[d]				
Higher than average	182	77.1	61.63	<0.001[f]
Same as average	324	66.1		
Lower than average	132	45.2		
Beliefs about social stigma[e]				
Genetic component increases stigma	338	70.9	29.22	<0.001[f]
No effect on stigma	153	54.6		
Genetic component decreases stigma	98	52.7		

[a] Refers to considered interest in genetic testing through a medical clinic.

[b] Refers to personal history of a mental illness (depression, bipolar disorder or schizophrenia).

[c] Refers to experience of depression, bipolar or schizophrenia through a close relative or close friend.

[d] Refers to personal estimation of risk for major depressive disorder compared to average population risk.

[e] Refers to belief that genetic evidence for mental illness would increase or decrease stigma. χ^2 values are from Pearson's χ^2 tests.

[f] p values <0.1 entered into logistic regression.

Interest in predictive genetic testing for depression risk by channel of access

Interest in depression-risk genotyping varied according to channel of access (doctor *versus* DTC on the internet) and before *versus* after consideration of positive and negative implications, information about which was provided during the telephone interview ('naïve interest' *versus* 'considered interest'). When naïve, 60% of participants were interested in depression-risk genotyping through a doctor, which marginally increased to 63% after consideration. When naïve, 49% of participants were interested in accessing the same test DTC on the internet, which significantly decreased to 40% once given the opportunity for consideration ($n = 981$, $\chi^2 = 476$, df = 1, $p < 0.001$). Interest in accessing depression-risk genotyping through a doctor was

significantly greater than interest accessing such a test DTC in both cases, when either naïve ($p < 0.001$) or considered ($p < 0.001$).

Factors associated with considered interest in predictive genetic testing for depression risk

Table 2 shows the results from bivariate analyses of factors associated with considered interest in depression-risk genotyping. Considered interest in depression-risk genotyping was significantly and positively associated with having a personal history of a mental illness; self-estimation of having a higher than average risk for major depressive disorder; being female; having no post-school education; endorsement of perceived benefits of having such a test; perceiving genetics, life stress and/or abuse as causal attributions

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Table 2(b). *Items assessed for association with considered interest[a] in depression-risk genotyping (maximum n = 1046)*

Variable	Interested in testing[a]		Not interested in testing[a]		z/t	p
	n	Mean (s.d.)	n	Mean (s.d.)		
Endorsement of benefits or disadvantages of testing[b]						
Endorse benefits	644	4.1 (0.5)	385	3.8 (0.7)	8.35	<0.001[d]
Endorse disadvantages	644	3.4 (0.8)	385	3.5 (0.8)	1.83	0.068[d]
Endorsement of causal attributions[b]						
Genetics	644	4.5 (0.9)	385	4.5 (1.0)	2.15	0.032[d]
Abuse	644	4.6 (0.6)	385	4.4 (0.8)	5.16	<0.001[d]
Life stress	644	3.7 (0.8)	385	3.9 (1.0)	5.15	<0.001[d]
Family environment	644	4.1 (0.9)	385	3.8 (1.0)	4.86	<0.001[d]
Gene–environment interaction	618	4.1 (0.7)	368	3.9 (0.8)	2.23	0.026[d]
Incomplete penetrance	597	4.0 (0.8)	359	3.9 (0.8)	1.18	0.238
No genetic factors	604	4.1 (0.8)	368	4.1 (0.7)	0.77	0.439
Age	643	50.5 (16.7)	384	50.9 (15.5)	0.39[c]	0.694

s.d., Standard deviation.

[a] Refers to considered interest in genetic testing through a medical clinic.

[b] Range 1 to 5, with higher values indicating greater endorsement. Values are absolute values from Mann–Whitney U tests.

[c] t value is from an independent samples t test.

[d] p values <0.1 entered into logistic regression.

Table 3. *Final model of logistic regression analysis predicting factors influencing interest[a] in having depression-risk genotyping after controlling for demographic factors (n = 930)*

Variable	B	OR	95% CI	p
Personal history of mental illness	0.95	2.58	1.66–4.00	<0.001
Self-estimation of risk for depression higher than average	0.65	1.92	1.52–2.42	<0.001
Endorsement of perceived benefits of depression-risk genotyping	1.24	3.47	2.57–4.66	<0.001
Endorsement of perceived disadvantages of depression-risk genotyping	−0.23	0.80	0.66–0.97	0.021
Belief that genetic evidence for mental illness will increase social stigma	0.48	1.62	1.34–1.96	<0.001
Age	−0.01	0.99	0.98–1.00	0.057
Sex	0.22	1.25	0.92–1.70	0.152
Education level	−0.183	0.83	0.61–1.14	0.249
Country of birth	−0.12	0.89	0.62–1.27	0.523

OR, Odds ratio; CI, confidence interval.

Final model: −2 log likelihood ratio = 1030.679, Cox and Snell R^2 = 0.189, Nagelkerke R^2 = 0.258, p < 0.001.

[a] Refers to considered interest in genetic testing through a medical clinic.

for mental illness; and perceiving gene–environment interaction as a causal mechanism. Among participants who thought evidence of a genetic component would affect stigma associated with mental illness, a significantly greater proportion believed stigma would increase rather than decrease (n = 670, 72% v. 28%, p < 0.001). Despite this, we found that considered interest in having depression-risk genotyping was significantly associated with beliefs that social stigma would increase.

When these variables were entered into a logistic regression model using a backward stepwise (likelihood ratio) elimination method (Table 3), personal history of mental illness [odds ratio (OR) 2.58, p < 0.001], higher than average self-estimation of risk for major depressive disorder (OR 1.92, p < 0.001), endorsement of benefits of testing for a depression-risk variant (OR 3.47, p < 0.001), and the belief that genetic evidence for mental illness would increase social stigma (OR 1.62, p < 0.001) were all significantly and positively associated with considered interest in depression-risk genotyping after controlling for sex, age, education level and country of birth. A significant negative predictor of interest was endorsement of perceived disadvantages of depression-risk genotyping (OR 0.80, p = 0.021).

Discussion

This large, national population-based study suggests that formal medical services are likely to be the preferred channel for accessing predictive genetic testing as demonstrated in this example of serotonin transporter genotyping for depression risk. This preference was significantly higher compared to interest in accessing genetic tests DTC after considering the benefits and disadvantages of predictive genetic testing. Nevertheless, considered interest in accessing such a test commercially prevailed, suggesting that concerns about the availability of unregulated DTC genetic testing need to be addressed. This finding supports results of our previous qualitative study, which demonstrated greater trust among participants in obtaining such a test through the medical system, with interest modified by concerns about genetic discrimination and loss of privacy (Wilde *et al.* 2010).

Of the 1029 participants who answered the question, 63% indicated considered interest in having predictive genetic testing for susceptibility to depression, if it were available. This level of interest is similar or marginally lower than that reported in previous studies that have demonstrated rates of interest in predictive genetic testing of 61% (Green *et al.* 2009), 69% (Jones *et al.* 2002), 83% (DeLisi & Bertisch, 2006; Laegsgaard *et al.* 2009) and 97% (Smith *et al.* 1996) for susceptibility to Alzheimer's disease, bipolar disorder (Smith *et al.* 1996; Trippitelli *et al.* 1998; Jones *et al.* 2002; Meiser *et al.* 2008), schizophrenia (Austin *et al.* 2006; DeLisi & Bertisch, 2006) and psychiatric disorders in general (Illes *et al.* 2003; Laegsgaard & Mors, 2008; Laegsgaard *et al.* 2009) in relatively small groups with direct experience of the illness including patients, relatives and professionals. The lower rate of interest demonstrated in this large national sample is likely to reflect a more realistic indication of community interest in predictive genetic testing for depression risk and other psychiatric conditions. Actual uptake of such testing once clinically available could be lower than predicted by intention to test (Lerman *et al.* 2002).

The present study identified strong positive significant associations between considered interest in genetic testing for susceptibility to depression and personal self-reported history of mental illness; a higher than average self-estimation of increased risk for major depressive disorder; endorsement of the perceived benefits of having such a test; and a belief that a genetic explanation for mental illness would increase social stigma linked with the disorder. These associations were independent of age, sex, level of education and country of birth.

The finding that perceived personal susceptibility to the disorder is a strong predictor of interest in predictive genetic testing is consistent with that reported for other multifactorial disorders such as heart disease (Sanderson *et al.* 2004), schizophrenia (DeLisi & Bertisch, 2006), bipolar disorder (Trippitelli *et al.* 1998; Jones *et al.* 2002; Meiser *et al.* 2008) and psychiatric disorders in general (Laegsgaard & Mors, 2008). However, predictors of uptake of predictive genotyping in clinical situations may differ. Uptake rates are likely to be influenced by differences in patient perceptions about predictive validity of the genetic test in question; potential benefits of such a genetic test, such as accessing early help; potential disadvantages such as employment and insurance discrimination; and differences in implications for members of affected families.

The finding of a significant positive association between considered interest in genetic testing for susceptibility to depression and endorsement of perceived benefits of having such a test, and a significant negative association with endorsement of perceived disadvantages, supports prevailing beliefs that perceived benefits may outweigh risks (Trippitelli *et al.* 1998). The most frequently rated perceived benefits, namely a greater preparedness for accessing early psychological help and minimizing stress, are consistent with beliefs reported in a previous study that such testing could facilitate prevention and earlier intervention of major depressive disorder (Wilhelm *et al.* 2009). The findings also confirmed perceptions that potential for discrimination by insurance companies or employers was the most frequently identified disadvantage of genetic testing for susceptibility to depression. Several governments have issued a ban on marketing genetic tests for common complex disorders directly to the consumer in the absence of appropriate regulation (ALRC, 2003; Hudson *et al.* 2007; Human Genetics Commission UK, 2007). Despite the signing of the Genetic Information Nondiscrimination Act (GINA) into law in 2008 in the USA, where many of the commercial vendors of DTC genetic tests are based, there may be no guarantees of protection against discrimination (Van Hoyweghen & Horstman, 2008). Considering DTC genetic tests are marketed internationally, consumers may have no legal protection from genetic discrimination for insurance or employment in their own country. The recent proposal to introduce a mandatory registry of genetic tests aims to overcome some of these problems and improve the genetic testing system by providing the public and health providers with accurate, reliable and validated information about the options available before decisions are made about obtaining a genetic test (Zonno & Terry, 2009). Thus, the study's findings highlight that, although predictive genetic testing as an intervention tool for target groups is likely to be

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acceptable to the general community, they indicate the need for appropriate legislation to prevent genetic discrimination if such interventions are to be effective.

Finding a significant positive association between beliefs that evidence of a genetic component for mental illness would increase rather than decrease social stigma and considered interest in having genetic testing for susceptibility to depression seems surprising at first. It could be that perceived benefits of genetic testing outweigh concerns about stigma, that major depressive disorder is perceived as less likely to have a genetic basis than other mental illnesses, or that there is less stigma attached to depression than bipolar disorder and schizophrenia.

It should be noted that the use of landline telephone numbers may have skewed the sample towards older age groups and females, consistent with reported participation bias in public health surveys (Purdie *et al.* 2002; Sogaard *et al.* 2004). The present study used strategies known to minimize self-selection bias caused by non-response, including randomization of participant selection per household, achieving a moderately high participation rate, and controlling the results for demographic confounders statistically (Mishra *et al.* 1993).

Other limitations relate to the possibility that some participants may have interpreted the term 'life stress' to mean everyday life stress rather than significant stressors associated with mental illness, such as child abuse, which could have affected interest in testing based on perceptions about the modifiable nature of risk factors. Attitudes towards genetic testing for susceptibility to a psychiatric disorder may be influenced by naivety about the low predictive power of such tests. The low risk rates for first-degree relatives for developing psychiatric disorders with incomplete penetrance compared with Mendelian traits should be kept in perspective when informing the public and designing mental health interventions.

Conclusions

This is the first study to provide data from a large national cohort in which the determinants of community interest in predictive genetic testing for mental illness and its psychosocial impacts have been investigated. Using the example of testing for a genetic variant for depression risk, the results indicate that there is likely to be strong interest in predictive genetic testing for a complex trait such as major depressive disorder if it were to become available, even though the predictive validity and clinical utility of such tests remain unclear. It is likely that interest will persist despite finding attitudes that genetic links to mental illness would increase rather than decrease stigma.

The study provides objective data in place of the current subjective commentaries on community concern about unregulated predictive genetic testing. Large population surveys such as that reported here are important in informing public debate, public education programmes and policymaking.

Declaration of Interest

None.

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