Developing A Brief Screening Instrument for Psychosocial Risk Associated with Genetic Testing – A Pan Canadian Cohort Study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-002227
Article Type:	Research
Date Submitted by the Author:	15-Oct-2012
Complete List of Authors:	Esplen, Mary Jane; Toronto General Hospital, Behavioural Science & Health Research Division; de Souza Institute, Cappelli, Mario; Children's Hospital of Eastern Ontario, ; University of Ottawa, Wong, Jiahui; de Souza Institute, ; University of Toronto, Department of Psychiatry Bottorff, Joan; University of British Columbia Okanagan, Hunter, Jon; Mount Sinai Hospital, ; University of Toronto, Department of Psychiatry Carroll, June; Mount Sinai Hospital, Dorval, Michel; Laval University, Wilson, Brenda; University of Ottawa, Allanson, Judith; Childrens Hospital of Eastern Ontario, Genetics Semotiuk, Kara; Mount Sinai Hospital, Zane Cohen Centre for Digestive Diseases Aronson, Melyssa; Mount Sinai Hospital, Zane Cohen Centre for Digestive Diseases Bordeleau, Louise; McMaster University, Charlemagne, Nicole; Toronto General Hospital, Behavioural Science & Health Research Division Meschino, Wendy; North York General Hospital,
Primary Subject Heading:	Genetics and genomics
Secondary Subject Heading:	Health services research
Keywords:	Genetics < TROPICAL MEDICINE, Cancer, Psychosocial, Screening, Psychosocial adjustment, behavioural science

Title

Developing A Brief Screening Instrument for Psychosocial Risk Associated with Genetic Testing – A Pan Canadian Cohort Study

Corresponding Author Address

Mary Jane Esplen, PhD
CIHR Scientist and Professor
Department of Psychiatry, Faculty of Medicine, University of Toronto
Behavioral Sciences and Health Research Division
University Health Network
200 Elizabeth Street, 9-EN-242A
Toronto ON M5G 2C4 Canada
Tel: (416) 340-3024
Fax: (416) 340-4739
Email: mesplen@uhnres.utoronto.ca

List of Authors and Institutions

Mary Jane Esplen PhD[1,2,3], Mario Cappelli PhD[4], Jiahui Wong PhD[2,3], Joan Bottorff PhD[5], Jon Hunter MD[2,6], June Carroll MD[6], Michel Dorval PhD[7], Brenda Wilson PhD[8], Judith Allanson MD[9], Kara Semotiuk MSc[10], Melyssa Aronson MSc[10], Louise Bordeleau MD[11], Nicole Charlemagne MSW[1], Wendy Meschino MD[12]

[1]Toronto General Research Institute, Toronto ON; [2]University of Toronto: Department of Psychiatry, Toronto ON; [3]de Souza Institute, Toronto ON; [4]Children's Hospital of Eastern Ontario, Ottawa ON; [5]University of British Columbia Okanagan, Kelowna BC; [6]Mount Sinai Hospital, Toronto ON; [7]Laval University, Quebec QC; [8]University of Ottawa, Ottawa ON; [9]Eastern Ontario Regional Genetics Centre, Ottawa ON; [10]Zane Cohen Centre for Digestive Diseases, Mount Sinai Hospital, Toronto ON; [11]McMaster University, Hamilton ON; [12]North York General Hospital, Toronto ON.

Keywords:

Genetics, Psychosocial, Screening, Psychosocial Problems, Psychosocial Functioning, Psychological Risk Factors

Word Count: 4616

Summary

1) Article Focus

- A significant group of individuals undergoing genetic testing for Adult onset disease experience distress or challenges in adaptation
- Current psychological screening tools do not take into consideration "risk factors" associated with heritable illness or genetic-related stressors
- A screening tool designed for genetic testing services is a useful tool to guide clinicians in relation to which patients would benefit from added psychosocial support during the genetic testing process.

2) Key Messages

- A subgroup of patients undergoing genetic testing required added psychosocial support to facilitate adaptation to genetic/ risk information. Busy genetic service providers can face challenges to identify these individuals and provide timely interventions or referrals.
- A new brief instrument was designed and validated to identify those individuals at psychological risk who are undergoing genetic testing for adult onset diseases.
- This is the first study to develop and validate a psychological screening instrument for genetic testing field.

3) Strengths and Limitations

- This newly developed tool, Genetic Psychosocial Risk Instrument (GPRI), is the first reported psychosocial screening instrument for use across Adult Onset Hereditary Diseases.
- The GPRI demonstrates promising psychometric properties as a tool designed to assist genetics health care providers determine which of their patients undergoing genetic testing for AOHD is at increased psychological risk and who will benefit from added psychosocial support.
- Study findings are limited by the characteristics of the sample, most participants were female and undergoing testing for BRCA1/2. Future studies could further address the validity of GPRI in male populations and in the rare adult onset hereditary diseases, such as Huntington's Disease.

Abstract:

Objectives: To develop a brief, reliable and valid screening instrument for use in the genetic testing context.

Design: A prospective two phase cohort study.

Setting: 5 genetic testing centres in primary care setting across Canada for Adult Onset Hereditary Disease (AOHD) such as cancer, Huntingtons, or Hemochromatosis.

Participants: 141 individuals were approached and consented to the instrument development phase of the study (Phase I). The Genetic Psychosocial Risk Instrument (GPRI) developed in Phase I was tested in Phase II for item refinement and validation. A separate cohort of 722 individuals consented to the study, 712 completed the baseline package, and 463 completed all follow up assessments. Most participants were female, at mid-life stage. Individuals in advanced stages of the illness or with cognitive impairment or language barrier were excluded.

Interventions: Phase I: GPRI items were generated from a review of the literature, and refined with input from health care providers and the first cohort of participants. Phase II: further item refinement and validation was conducted with a second cohort of participants who completed the GPRI at baseline and were followed for psychological distress one month post genetic testing results.

Primary and secondary outcome measures: GPRI, Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), Brief Symptom Inventory (BSI), and Impact of Event Scale (IES).

Results: The final 20 item GPRI had a high reliability with a Cronbach's Alpha at 0.81. The construct validity was supported by high correlations between GPRI and BSI and IES. The predictive value was demonstrated by a Receiver Operating Characteristic (ROC) curve of 0.78 plotting GPRI against follow up assessments using HAM-D and HAM-A.

Conclusions: With a cut off score of 50, GPRI identified 84% of participants who displayed distress post genetic testing results, supporting its potential usefulness in a clinical setting.

Word count: 297

Trial registration: Not applicable

INTRODUCTION

Genetic predisposition is an important determinant of chronic disease and disability. Despite the benefits of genetic testing, such as increased screening or prophylactic interventions, individuals at high risk for serious illness may become increasingly fearful, worried or distressed about the future. In fact, a consistent finding is that the majority of individuals do adjust to genetic test results, however a subset of individuals undergoing genetic testing for Adult Onset Hereditary Disease (AOHD) experience psychological distress. A screening tool, designed for the genetics testing context, would be ideal to assist health care providers to identify this particular group in a timely manner in order to provide appropriate preventive care or follow up interventions. Herein, we present a newly developed psychological risk screening instrument that can be readily used within a genetic service for AOHD.

Risk Factors and Psychological Impact of Genetic Testing: The Evidence

The knowledge of genetic risk is life-long and individuals and families often find themselves confronted with ongoing need to face issues and make decisions. Examples include decisions about prevention and treatment options (e.g. increased surveillance, prophylactic surgery, chemoprevention), test result notification to family members, and relationship decisions (i.e. marriage, childbearing) [1, 2]. Studies utilizing standardized measures of distress have demonstrated that 8 to 25% of individuals undergoing genetic testing experience distress, the level of which falls within the clinical ranges for depression and anxiety [2-5]. Studies that have utilized standardized disease specific measures of distress (i.e. cancer worry scales) have demonstrated significantly somewhat higher prevalence levels [6, 7].

The risk factors for psychological distress amongst individuals undergoing genetic testing have been delineated in several studies [4, 8, 9]. While there is generally elevated distress among those who receive positive test results [9-11], individuals testing negative or receiving uninformative results may also have adjustment difficulties [12]. For example, individuals may feel guilt or continue to worry about their disease risk [2, 7, 12]. These findings highlight the importance of considering risk factors in addition to the test result itself. Individuals who have elevated distress at the pre test stage and those with a previous psychiatric history (i.e., depression) are particularly at risk for an adverse psychological outcome after testing [2, 8, 9].

Additional risk factors for distress are more specific to the genetics context and include the level of penetrance of the gene mutation or degree of certainty of developing the disease [4]. The perception of control over the disease (including the number of prevention/treatment options) and perception of the immediacy of risk (proximity in age to perceived disease onset) are important predictors [4, 13]. The expectation of a negative test result can play a role in adjustment, as can the context of test results of other family members [9, 14]. As in other medical areas, specific coping styles can affect adjustment [15]. The prior experiences with loss of family members to disease, as well as the developmental level (i.e. young age) of the individual at the time of the loss [2, 3, 16] are significant factors affecting potential adjustment. In addition, the prior experience of giving care to a family member with the disease and lower levels of social support have been associated with poorer adjustment following a positive test result [2-4, 8, 16].

It is clear that there is not one predominant factor, but rather, a series of variables that may contribute to elevated levels of psychological distress [2, 17]. Emotional reactions may impede the assimilation of risk information and the adoption of preventive measures [2, 18].

Psychological distress occurs along a continuum [19, 20] and can be difficult to identify by health professionals [21]. Distress may not become manifest to the health care team until the patient reaches an observable crisis level, i.e. the onset of severe depression or anxiety, or significant conflicts with the family. An early screening instrument would enable healthcare providers to identify patients being at higher psychological risk in order that appropriate support can be given at the right time. In fact, there is now a general consensus that genetic testing should be accompanied by psychological support to promote optimal adjustment [2, 22].

Screening for Psychological Risk Factors- Why is it necessary?

The gold standard for identifying psychologically distressed individuals involves structured clinical interviews administered by a clinical psychologist or psychiatrist [21]. However, it is too costly and often not feasible in genetic clinics. Standardized measures of psychological functioning can also be used as a method for identifying distress. However, few clinics use these measures in practice because of personnel and time requirements for scoring and interpretation of them. Furthermore, these instruments tend to identify global symptoms that are consistent with the diagnostic classifications of anxiety and/or depression and may lack sensitivity to the important and unique issues that surround genetic testing; issues that may include concerns about family members, past experiences with an inheritable disease, and uncertainty about risk reduction options [19, 21]. In addition, items on these measures typically focus on symptoms of anxiety or depression, rather on variables associated with heritable disease or genetic testing or risk, which may pose barriers for use by genetics health service providers who may prefer instruments that at face value, appear to them and their patients as being more relevant to the genetic testing context.

More recently, new outcome measures designed to assess the psychological impact of receiving genetic information have been developed. For example, the MICRA- is designed to assess concerns and impacts associated with genetic testing for BRCA1/2 [19] and the Psychological Adaptation to Genetic Information Scale is now available [23]. While these measures will require further validation, they provide more clinically relevant approaches to capturing specific impacts of genetic information, such as the sense of increased vulnerability and continued uncertainty often experienced following genetic testing [19, 23].

Measures of global psychological functioning and the evolving outcome measurement tools for the genetics field are not designed to "predict" vulnerability for future distress, but rather, measure current distress levels. Screening, in contrast, is a rapid, cost-effective alternative [21] to prospectively identify individuals who may experience significant difficulty in their attempts to adapt to their genetic information and any associated treatment options [17]. A screening tool enables providers to offer timely and focused educational and psychosocial interventions to prevent future distress.

The primary *objective* of this study was to develop a brief, reliable and valid screening instrument for use in the genetic testing context. The new instrument aimed to incorporate empirically based risk factors for psychological distress and would need to show a high sensitivity, specificity and predictive validity indicating risk for future distress post genetic testing results. A cutoff point would be determined to guide clinical decisions as to whether or not to refer, further assess, or intervene to reduce an individual's expressed concern.

METHODS AND MATERIALS

The study was carried out from September 2005 to July 2010, with research ethics board approval from participating genetics clinics: Toronto (Mount Sinai Hospital, North York General Hospital, Princess Margaret Hospital); Ottawa (Children's Hospital of Eastern Ontario); and Vancouver (British Columbia Cancer Agency). Individuals beginning the genetic testing process for AOHD at each site were approached by genetic counsellors on the project team for their permission to be contacted about the study. Those who expressed interest were mailed the baseline package that included the informed consent. The informed consent included all components of the study, including questionnaires, follow-up phone calls, telephone interviews, as well as to the release of their genetic testing information to the research team.

A two phase approach was used for this study**: *Phase I:*** *Item Generation and Refinement,* and ***Phase II:*** *Validation*. The multi-stage method [24] takes validation into consideration at each stage of scale development and has been used successfully in previous studies [25].

Phase I: Item Generation and Refinement.

Item generation

To generate items for the Genetic Psychosocial Risk Instrument (GPRI), a literature search was performed for the following AOHDs: Cancer (Hereditary Breast-Ovarian Cancer Syndrome/ Lynch Syndrome), Huntington Disease (HD), and Hemochromatosis. These diseases were selected as they represented the majority of patients attending genetic clinics and had an associated available psychosocial literature for review. Databases including Cinahl (1982 to 2006), Medline (1966 to 2006), PsychInfo (1985 to 2006), and Pubmed (1985 to 2006) were searched as well as hand search of references from major publications. Keywords included: genetic screening, genetic testing, psychological, psychological well-being, psychological

adjustment, stress, adaptation, cancer worry, disease worry, psych functioning, and distress. Selection criteria for the literature review included studies with a follow up design or review articles. Each selected study was reviewed by two reviewers on its quality of evidence and generalizability using a standardized template. A total of 73 relevant studies were identified among the disease groups: 49 on cancer, 20 on HD, 2 on Hemochromatosis, and 2 described mixed conditions.

Risk factors for psychological distress identified by the literature review provided the basis for item generation. Items were written in a mixed format where respondents were asked for their endorsement of each statement ranging from Yes/No for risk factors of binary nature, to a 5 point likert-type scale for risk factors with stages in frequency and/or intensity. The instrument items were further refined by genetic service providers rating items on *comprehension, readability, and perceived clinical relevance* using a ten-point scale with 0 being "excellent/definitely relevant" and 10 being "very poor/definitely not relevant". Risk factor items were removed if it was rated below five. Providers were also asked to suggest additional risk factor items. These suggestions were checked against the literature for empirical evidence. Following this step, 7 volunteers undergoing genetic testing for AOHDs were recruited to try out the scale for clarity, succinctness and relevance from the clients' perspectives. At this stage, the proposed instrument consisted of 56 items: demographics (4 items); perceived risk (8 items); life events and family history of the disease (8 items); perceived impact of carrying a mutation (9 items); family communication (6 items); disease specific concerns (5 items); optimism (3 items); social support (3 items), pre-morbid functioning and previous psychiatric history (10 items).

Item refinement:

Subjects: Following informed consent, a convenient sample of 141 participants who had given blood for genetic tests at the Toronto and Ottawa sites completed the GPRI (using a three patients per item ratio) to select the best items for the candidate scale. The participants were middle aged (48.67 + 13.29), mostly female (77%) testing for hereditary breast cancer, and many (65%) had already suffered the onset of the illness.

Scoring: To ensure that binary items carry an equal weight as the 5 point likert-type items, a score of 5 was assigned to *Yes* and 1 to *No*. A score of 3 or mean-substitute was assigned to *Not Applicable* to allow it to be counted in the total score. Reliability analysis was carried out and a Cronbach's Alpha was set for .75 or higher for the scale to move to the next phase [26]. Any item with an item-total correlation less than .20 was identified for potential removal. Using team consensus, a total of 19 items were removed, combined or substituted, resulting in a 37 item GPRI candidate scale at the end of phase I.

Phase II: Scale Validation

Subjects: Individuals undergoing genetic testing for one of the AOHDs in each of the five study sites were invited to participate in the study. To be included individuals needed to be: 1) age 18 or above undergoing genetic testing for cancer, HD, or Hemochromatosis; 2) fluent in English; and 3) residing within 1.5 hours driving distance from study site. Although the onset of an AOHD was not an exclusion criterion, individuals in advanced stages of the illness and / or who were unable to consent due to cognitive impairment were excluded. Participants were asked to complete a set of questionnaires described below within a one month period following the provision of a blood sample and while awaiting test results. Within two weeks to one month post

genetic test results, participants were mailed the follow-up questionnaires and received a telephone interview from the project team for the assessment of distress.

Materials**:** At baseline, three psychosocial measures were used: *GPRI Candidate Scale* from Phase I. To facilitate scoring of the scale by genetic providers, scores for response to each item on the GPRI are imbedded in the questionnaire, where clinicians can calculate a total score in less than 5 minutes. *Brief Symptom Inventory* (BSI) The BSI is a 53-item measure of psychological distress that contains three global scales i) depression, ii) anxiety and iii) somatization [27]. It is widely used in medical and psychiatric populations to assess psychological functioning; *Impact of Event Scale (IES)*: The IES is a 15-item, likert-style scale used to assess the experience of stress and is designed to be easily anchored to have individuals report on items in relation to a specific stressor or life event (i.e. the stress of a positive genetic test result). It has two sub-scales: i) intrusive thoughts and feelings associated with the stressful life event, and ii) items associated with patterns of avoidance of certain thoughts, feelings, or situations [28].

Measures at one month post genetic testing results included: the BSI, IES and the telephone based Hamilton Depression 29-item Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A). The HAM-D evaluates depressed mood, vegetative and cognitive symptoms of depression, and comorbid anxiety symptoms [29]. The HAM-A quantifies the severity of anxiety symptomatology and consists of 14 items. The HAM-D and HAM-A have demonstrated validity in clinical interview, in person or by telephone [30]. The one-month follow-up time point was selected as it is when elevated distress might occur [31]. In addition, the 2-week duration criterion for depression defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) is met by this time frame.

Assessing Psychometric Property of the Scale

As a first step, items were required to have at least an 80% response rate. Second, each item was examined to determine its contribution to the internal consistency of the total 37-item scale. The minimum item-total correlation was set at .20 [32].

A principal components factor analysis with varimax rotation was performed on the candidate scale to examine the factor structure and the loading of the items. To assess the *convergent validity* of the candidate scale, the correlations between baseline GPRI, IES and BSI were calculated. To assess the *sensitivity, specificity and predictive value* of the GPRI, the follow up HAM-D and HAM-A were used to identify "cases". For example, participants with a high GPRI at baseline would be classified as "at risk" for future onset of adjustment difficulties. This would be confirmed by a high HAM-D or HAM-A score or "cases" during 1 month follow up; those with low GPRI should receive low score in HAM-D or HAM-A as "non-cases". The predictive value of the GRPI, describing the number of test-positives (in our case, high GPRI) who truly have the psychological condition (i.e. cases identified by HAM-D or HAM-A), was tested by a Receiver Operating Characteristic (ROC) curve which visually plotted the true positive rate (sensitivity) over false positive rate (1-specificity).

To address the issue of missing follow up data in a cohort study, as suggested in the literature [33], we tested the assumption that the sub sample with missing data had a similar baseline exposure (similar GPRI) as the non-missing subsample by comparing baseline GPRI between the two groups. This step assesses if there was systematic bias resulting from the loss of information in the follow up period.

RESULTS

Participant characteristics

Study packages were mailed to 1129 individuals interested in hearing more about the study. Of these individuals, 722 of them consented and 712 (98%) completed the GPRI. Most participants were tested for the inheritable cancers, while a small percentage of participants were tested for hemochromatosis and HD. Similar to phase I, phase II participants were mostly female, at mid-life stage, and more than half had a past diagnosis of the disease (see table 1).

Insert Table 1 about Here

Of the 712 participants, 620 (86%) individuals were contacted during the one month post genetic testing results follow-up phase. Among them, 481 (67%) completed IES and BSI self report and 463 (65%) who were successfully contacted completed a standardized telephone interview using HAM-D and HAM-A (up to 4 telephone calls were made).

Baseline GPRI score of the 249 individuals with missing follow up data was compared with the 463 individuals with complete data (49.5±13.09 versus 49.1 ±13.53 respectively, p=0.74). Because of the similarity between the two subsamples, we proceeded with reliability and validity analysis of the tool using the subsample that provided outcome data.

We carried out the calculation of depression and anxiety rate using follow up IES and BSI data. About 13.0% to 20.1% of participants reached the threshold of moderate to severe distress respectively (see table 2).

Insert Table 2 about Here

HAM-D and HAM-A interview data from 463 participants were used as a validation tool to measure distress post genetic testing results. The literature suggests that the observer-rating scales should be used over subjective report scales as the principal outcome criterion in psychological distress both in general practice and in research trials [34]. Defined by HAM-D >=12 [35] or HAM-A >=10 [36], the rates for distress was 13.7%. The rate was 13% for HD, 15% for breast cancer and 7% for Lynch Syndrome.

Reliability and Factor Analysis

A reliability analysis was performed on 37 items. Twenty items were selected based on the criteria for item selection described in the methods section. The Cronbach's alpha of the 20 item GPRI was 0.81 suggesting a good level of internal consistency.

The factor analysis resulted in a psychometrically sound 3-factor solution, with subscales representing the dimensions of: 1) Perceived impact and personal adjustment to genetic testing (10 items); 2) Past history of mental health concerns (5 items) and 3) Personal history/family history/loss to cancer (3 items). All three factors met the minimum Eigenvalue criteria of 1.

The first, 12-item factor (ALPHA = 0.85), accounting for 22% of the variance, includes items associated with the anticipated or experienced impact of being at high risk for AOHD. Example items included: "My worries about the disease affect my daily mood"; "The disease for which I am at risk is currently causing a significant disruption in my family life".

The second 5-item factor (ALPHA = 0.76), accounted for an additional 14% of the total variance, and reflected a sense of a person's past history or vulnerability of mental health issues,

e.g. “I have had emotional problems in the past”, These items have been used in other medical health areas [37, 38] and tend to be predictive of maladjustment [20] following a life event.

The third 3 item factor (ALPHA = 0.08), accounted for 8% of the total variance and included a personal or family history of the genetic disease being tested in the clinic. Examples include: “I have a personal diagnosis of the disease for which I am receiving counseling”; “I lost a close family member to the disease for which I am receiving counseling”; and “I have taken care of a very ill parents or another close family member”. These three final items had low item total correlation because they were different from the rest of the items in that they focused on description of personal history, rather than psychosocial-related items. These items were kept in the scale as they contributed significantly to the overall variance, and correlated highly with HAM-D and HAM-A. To determine the relationships between the three factors/subscales, correlations were computed. Factor1 and factor2 had moderate correlations with each other (factor1/factor2 $r=0.30$, $p<0.01$). The correlation of the first two factors with factor3 was much lower as expected (factor1/factor3 $r=0.06$, and factor2/factor3 $r=0.01$, not statistically significant). These results support the multidimensional character of the GPRI scale (see Table 3).

Insert Table 3 about Here

The total score for the 20 item GPRI ranged from 20 to 100, with a sample mean 49.36 ± 13.23. The total was calculated by the sum of the raw scores for each of the statements. Females had a significantly higher score for the GPRI than males (50.37 ± 13.14 vs 41.91 ± 11.47, $p<0.01$), and

participants testing for HD had a higher but non-significant score than participants testing for cancer (52.24±13.24 vs 49.37±13.22, n.s.).

Validity

Construct validity – correlations: The GPRI was assessed for its correlation with other standardized measures of psychological functioning at baseline. Convergent validity was demonstrated by the correlation between the GPRI and the following measures: a positive correlation with the IES total score at r = .51, p< .001, and with BSI at r = .58, p< .001.

Sensitivity, specificity and the predictive value of GPRI for future distress: The HAM-D and HAM-A were used to identify distress during the one month post genetic testing follow up. A total of 63 "cases" (13.6% of 463 completers) were identified as having psychological distress levels above threshold. Of these 63 cases, 55 reported genetic testing results: 18 positive, 26 negative and 11 uninformative. This is equivalent to 23% among participants testing positive, 10% among those with negative results, and 20% among uninformative. Participants scoring above HAM-D (N=55) threshold had significantly higher GPRI scores than participants below the threshold (N=408) (61.12±13.27 vs. 47.91±12.27, p<0.01). Same patterns were observed for HAM-A high (N=40) vs. low (N=423) (62.53±12.92 vs. 48.25± 12.43, p<0.01).

The predictive value of a test describes how many of the test-positives (in this case, a high score on GPRI) truly have the psychological condition. An ROC curve was used to plot the true positive rate (sensitivity) over the false positive rate (1-specificity). A good ROC curve rises sharply, indicating a high proportion in true positive and a low proportion of false positives. The

ROC curve for the GPRI was 0.78, which is considered as an indicator of an adequate screening instrument [39].

An important purpose of the GRPI in our study was to identify individuals at risk for post genetic testing psychological distress. Therefore, the cutoff value was set to maximize sensitivity – in another word, not to miss detecting a "case". Using a GPRI cut off score of 50, the instrument was able to predict 84% of the "cases" identified by HAM-D or HAM-A conducted post genetic testing results, with a specificity value of 60% (Figure 1).

Insert Figure 1 about Here

DISCUSSION

The aim of this study was to develop a brief, easy-to-use psychosocial screening instrument specific for the genetic testing context and to examine its reliability and validity (Appendix A). To our knowledge this is the first report of a psychosocial screening instrument for use across AOHD. Unlike current psychological instruments used mainly in research studies in genetics clinics to identify existing symptoms of depression and anxiety, or impacts, the GPRI assesses psychological risk factors, such as anticipated impacts of a genetic testing result and the perception of the disease. The GPRI demonstrates promising psychometric properties as a tool designed to assist genetics health care providers determine which of their patients undergoing genetic testing for AOHD is at increased psychological risk and who will benefit from added psychosocial support.

A high reliability was demonstrated by a Cronbach's Alpha at 0.81, moderate to high item-total correlation and inter-item correlation of the whole scale. The construct validity of the

scale was supported by high correlations between the GPRI and standardized psychological measures (BSI, IES). The clinical utility and predictive value of the GPRI was supported as well. A GPRI score above the cutoff of 50 at baseline was able to predict 84% of "distress" cases identified by HAM-D or HAM-A, a strong indicator of its potential usefulness in a clinical setting.

A brief self-administered screening questionnaire will be easy to incorporate into genetics clinics; the GPRI can be completed and scored quickly during clinical visits and without additional burden to patients and health providers. In addition, by focusing specifically on known risk factors associated with inheritable illness, the instrument will be perceived as being more clinically relevant and acceptable to patients. Patients with higher scores on the GPRI can be flagged and either receive telephone follow up to further assess concerns or potential distress, or be invited back for an appointment for further assessment treatment.

Alternatively, genetic counselors or geneticists with available psychosocial personnel could make a referral for a more formal psychosocial assessment to further explore and address the specific psychological factors self-reported. For example, in the case where an individual is particularly fearful of developing an illness or is concerned about specific impacts, such as expecting relationship or family communications difficulties, or for those with a past history of psychological illness, a psychologically trained health professional could employ cognitive-behavioral strategies to address ongoing anxiety, or provide psychological treatment to address any psychiatric symptoms (i.e. depression) [40]. Furthermore, several items incorporate variables related to heritable disease experiences or their perceptions, and the scale appeared acceptable to patients, demonstrating face validity in such a way that it may be more user friendly for the non-mental health professional, compared for example, to a standardized

psychological instrument on depression. The GPRI could be considered a "communimetric measures", that is, the items themselves are useful for the clinician in communicating concerns about specific areas of functioning directly with the patient. For example, if item 6 is endorsed by the patient as "strongly agree", the clinician can further explore the patient's concern and help identify the need for further clinical services [41].

Left untreated, significant levels of distress may lead to lower quality of life [40], or potentially lower satisfaction with genetics services [21]. A screening approach allows both for careful monitoring during a known stressful period-that of awaiting test results [42], and an opportunity for planned follow up and optimal use of limited psychosocial resources [2, 20, 21].

Our study findings are limited by the characteristics of the sample, in that most participants were female and undergoing testing for *BRCA1/2*. This pattern is similar to that observed in the literature on genetic testing for AOHD, which is predominantly focused on Hereditary Breast-Ovarian Cancer Syndrome. We attempted to obtain a larger sample of individuals undergoing genetic testing for HD or Lynch Syndrome which would presumably provide a greater sample of males. However, these sample pools were much smaller. This study and the GPRI represents a start to developing a general tool, since our belief and the literature suggests that these mental health issues or adjustment risk factors are not disease specific. We suggest that future studies address the validity of GPRI in male populations and in the rare adult onset hereditary diseases, such as HD. Future studies should also include randomized controlled trials to assess the effectiveness of the GPRI in predicting distress, the impact of the instrument on referral patterns, patient and provider satisfaction, and provider knowledge and skill in identifying and managing psychosocial distress, and on cost-effectiveness. The GPRI will also

need to be evaluated in primary care settings where genetics services might be offered more frequently to meet the demand.

CONCLUSIONS

This is the first study to develop a screening tool specifically to help identify individuals undergoing genetic testing for AOHD who are at increased psychological risk. The study resulted in an easy to use, 20-item scale consisting of 3 factors with promising psychometric properties. The GPRI has the potential to be used as a clinical screening tool and as a validated measure for future studies. Future work can examine its impact on clinical referral patterns within the field of genetics, and on its acceptability, reliability and validity with larger samples of individuals undergoing genetic testing for HD, Lynch Syndrome, and potentially for emerging new genetic tests, such as for cardiac or psychiatric disorders.

Acknowledgement

The first author is a recipient of a career scientist award from the Canadian Institutes of Health Research (CIHR) and the Ontario Women's Health Council. This study was funded by Canadian Institutes of Health Research (CIHR) Grant No. AHC 73144. We would like to express our gratitude to all the genetic testing patients who participated in our study. Thank you for your contribution towards this very important work and the development of the instrument. Thank you also to the genetic counselors and clinic staff from the participating genetic centers who assisted in recruitment: Children's Hospital of Eastern Ontario (Eastern Ontario Regional Genetics Centre); North York General Hospital (Clinical Genetics); Mount Sinai Hospital (Familial GI Cancer Registry & Familial Breast Cancer Clinic); Princess Margaret Hospital (Familial Breast & Ovarian Cancer Clinic); and BC Cancer Agency (Hereditary Cancer Program). We would also like to acknowledge and thank the research staff for their commitment and hard work to complete this national multi-site study. Finally, the team would like to pay special recognition to the late Dr. Anne Summers, who was co-investigator on the team. Her dedication to the need for empirically based tools and her strong vision to support recipients of new genetic technology were key influences in the conceptualization, funding and completion of this study.

Ethics: Research Ethics Board approval was obtained at all five participating sites: Toronto (Mount Sinai Hospital, North York General Hospital, Princess Margaret Hospital); Ottawa (Children's Hospital of Eastern Ontario); and Vancouver (British Columbia Cancer Agency).

Data Sharing Statement: There is no additional data available

Conflict of Interest: The authors do not have any conflict of interest to disclose.

Funding: This study was funded by Canadian Institutes of Health Research (CIHR) Grant No. AHC 73144.

Contributorship Statements

Dr. Mary Jane Esplen
Principal Applicant responsible for leading all aspects of the research, oversees budget, hiring staff, supervising data collection, analysis and interpretation, and writing of all manuscripts and reports.

Dr. Mario Cappelli
Co-principal inv. responsible for assisting in item generation and refinement, the implementation of data collection, interpretation of findings and writing of manuscripts and reports.

Dr. Jiahui Wong
Co- Applicant responsible assisting in instrument development, statistical procedures, sampling and interpretation of findings and writing of manuscripts and reports.

Dr. Joan Bottorff
Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services, development of guidelines and writing of manuscripts and reports.

Dr. Jon Hunter
Co-Applicant responsible for assisting in item generation and refinement, guideline development, interpretation of findings and writing of manuscripts and reports.

Dr. June Carroll
Co-Applicant responsible for assisting in item generation and refinement, implementation of the screening validation strategy and development of guidelines, interpretation of findings and writing of manuscripts and reports.

Dr. Michel Dorval
Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services, interpretation of findings and writing of manuscripts and reports.

Dr. Brenda Wilson
Co-Applicant responsible for co-leading the implementation of the consensus guidelines components of the proposed study. Will assist in item generation for tool, interpretation of findings, writing of manuscripts and reports.

Dr. Judith Allanson
Co-Applicant responsible for refining of items, guiding the recruitment of providers/patients and testing of the instrument in genetic services, development of guidelines and writing of manuscripts and reports.

Ms. Kara Semotiuk
Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services and development of guidelines, and writing of manuscripts and reports.

Ms. Melyssa Aronson
Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services, development of guidelines and writing of manuscripts and reports.

Dr. Louise Bordeleau
Co-Applicant responsible for overseeing recruitment at MSH and UHN site in Toronto, testing of instrument and interpretation of findings, writing of manuscripts and reports.

Ms. Nicole Charlemagne
Project coordinator, responsible for: patient recruitment and follow-up; assisting in item generation, refinement, and overall layout and design of tool; data collection, data entry, and data clean-up; revisions and submission of manuscript.

Dr. Wendy Meschino
Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services, interpretation of findings and writing of manuscripts and reports.

REFERENCES

1. Lerman C, Croyle RT. Emotional and behavioral responses to genetic testing for susceptibility to cancer. *Oncology (Williston Park)*. 1996;**10**:191-5, 9; discussion 200-2.

2. Bleiker EM, Hahn DE, Aaronson NK. Psychosocial issues in cancer genetics--current status and future directions. *Acta Oncol*. 2003;**42**:276-86.

3. Wellisch DK, Lindberg NM. A psychological profile of depressed and nondepressed women at high risk for breast cancer. *Psychosomatics*. 2001;**42**:330-6.

4. Broadstock M, Michie S, Marteau T. Psychological consequences of predictive genetic testing: a systematic review. *Eur J Hum Genet*. 2000;**8**:731-8.

5. Ho SM, Ho JW, Bonanno GA, et al. Hopefulness predicts resilience after hereditary colorectal cancer genetic testing: a prospective outcome trajectories study. *BMC Cancer*. 2010;**10**:279.

6. Trask PC, Paterson AG, Wang C, et al. Cancer-specific worry interference in women attending a breast and ovarian cancer risk evaluation program: impact on emotional distress and health functioning. *Psychooncology*. 2001;**10**:349-60.

7. Coyne JC, Kruus L, Racioppo M, et al. What do ratings of cancer-specific distress mean among women at high risk of breast and ovarian cancer? *Am J Med Genet A*. 2003;**116A**:222-8.

8. Marteau TM, Croyle RT. The new genetics. Psychological responses to genetic testing. *BMJ*. 1998;**316**:693-6.

9. Meiser B. Psychological impact of genetic testing for cancer susceptibility: an update of the literature. *Psychooncology*. 2005;**14**:1060-74.

10. Hamilton JG, Lobel M, Moyer A. Emotional distress following genetic testing for hereditary breast and ovarian cancer: a meta-analytic review. *Health Psychol*. 2009;**28**:510-8.

11. Shaw C, Abrams K, Marteau TM. Psychological impact of predicting individuals' risks of illness: a systematic review. *Soc Sci Med*. 1999;**49**:1571-98.

12. Dorval M, Gauthier G, Maunsell E, et al. No evidence of false reassurance among women with an inconclusive BRCA1/2 genetic test result. *Cancer Epidemiol Biomarkers Prev*. 2005;**14**:2862-7.

13. Cameron LD, Sherman KA, Marteau TM, et al. Impact of genetic risk information and type of disease on perceived risk, anticipated affect, and expected consequences of genetic tests. *Health Psychol*. 2009;**28**:307-16.

14. Smith KR, West JA, Croyle RT, et al. Familial context of genetic testing for cancer susceptibility: moderating effect of siblings' test results on psychological distress one to two weeks after BRCA1 mutation testing. *Cancer Epidemiol Biomarkers Prev*. 1999;**8**:385-92.

15. Dougall AL, Smith AW, Somers TJ, et al. Coping with genetic testing for breast cancer susceptibility. *Psychosom Med*. 2009;**71**:98-105.

16. Esplen MJ, Urquhart C, Butler K, et al. The experience of loss and anticipation of distress in colorectal cancer patients undergoing genetic testing. *J Psychosom Res*. 2003;**55**:427-35.

17. Zabora JR. Screening procedures for psychological distress. In: Holland JC, editor. Psycho-Oncology. New York: Oxford University Press; 1998. p. 653-62.

18. Watson M, Lloyd S, Davidson J, et al. The impact of genetic counselling on risk perception and mental health in women with a family history of breast cancer. *Br J Cancer*. 1999;**79**:868-74.

19. Cella D, Hughes C, Peterman A, et al. A brief assessment of concerns associated with genetic testing for cancer: the Multidimensional Impact of Cancer Risk Assessment (MICRA) questionnaire. *Health Psychol*. 2002;**21**:564-72.

20. Zabora J, BrintzenhofeSzoc K, Curbow B, et al. The prevalence of psychological distress by cancer site. *Psychooncology*. 2001;**10**:19-28.

21. Thewes B, Meiser B, Tucker K, et al. Screening for psychological distress and vulnerability factors in women at increased risk for breast cancer: A review of the literature. *Psychology, Health & Medicine*. 2003;**8**:289-303.

22. Howell D, Keller-Olaman S, Oliver T, et al. A Pan-Canadian Practice Guideline: Screening, Assessment and Care of Psychosocial Distress (Depression, Anxiety) in Adults with

Cancer. Toronto: Canadian Partnership Against Cancer (Cancer Journey Action Group) and the Canadian Association of Psychosocial Oncology2010.

23. Read CY, Perry DJ, Duffy ME. Design and psychometric evaluation of the Psychological Adaptation to Genetic Information Scale. *J Nurs Scholarsh*. 2005;**37**:203-8.

24. Jackson D. A sequential system for personality scale development. In: Spielberger C, editor. Current Topics in Clinical and Community Psychology. New York: Academic Press; 1970. p. 61-96.

25. Stuckless N, Goranson R. The vengeance scale: Development of a measure of attitudes toward revenge. *Journal of Social Behavior and Personality*. 1992;**7**:25-42.

26. Briggs SR, Cheek JM. The role of factor analysis in the development and evaluation of personality scales. *Journal of Personality*. 1986;**54**:106-48.

27. Derogatis LR. The brief symptom inventory (BSI). Administration, Scoring and Procedures Manual. 3rd ed. New York: National Computer Systems; 1993.

28. Horowitz MJ, Wilner N, Alvarez W. Impact of Events Scale: A Measure of Subjective Stress. *Psychosomatic Medicine*. 1979;**41**:209-18.

29. Hamilton MA. A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*. 1960;**23**:56-23.

30. Katzelnick DJ, Simon GE, Pearson SD, et al. Randomized trial of a depression management program in high utilizers of medical care. *Arch Fam Med*. 2000;**9**:345-51.

31. DudokdeWit AC, Tibben A, Duivenvoorden HJ, et al. Predicting adaptation to presymptomatic DNA testing for late onset disorders: who will experience distress? Rotterdam Leiden Genetics Workgroup. *J Med Genet*. 1998;**35**:745-54.

32. Walsh W, Betz N. Tests and Assessments. New Jersey: Prentice Hall Inc; 1985.

33. Melnick EL, Everitt BS. Quantitative risk analysis and assessment. Hebokea NJ: John Wiley & Sons; 2008.

34. Moller HJ. Rating depressed patients: observer- vs self-assessment. *Eur Psychiatry*. 2000;**15**:160-72.

35. Aben I, Verhey F, Lousberg R, et al. Validity of the beck depression inventory, hospital anxiety and depression scale, SCL-90, and hamilton depression rating scale as screening instruments for depression in stroke patients. *Psychosomatics*. 2002;**43**:386-93.

36. Pasquini M, Biondi M, Costantini A, et al. Detection and treatment of depressive and anxiety disorders among cancer patients: feasibility and preliminary findings from a liaison service in an oncology division. *Depress Anxiety*. 2006;**23**:441-8.

37. Beck CT. A checklist to identify women at risk for developing postpartum depression. *J Obstet Gynecol Neonatal Nurs*. 1998;**27**:39-46.

38. Reid AJ, Biringer A, Carroll JD, et al. Using the ALPHA form in practice to assess antenatal psychosocial health. Antenatal Psychosocial Health Assessment. *CMAJ*. 1998;**159**:677-84.

39. Goutham R. What is an ROC curve? *The Journal of Family Practice*. 2003;**52**:695.

40. Esplen MJ, Hunter J. Therapy in the Setting of Genetic Predisposition to Cancer' in 'Handbook of Psychotherapy in Cancer Care. In: Watson M, Kissane D, editors. Handbook of Psychotherapy in Cancer Care. London: John Wiley & Sons Ltd; 2011. p. 201-12.

41. Lyons JS. A Communication Theory of Measurement in Human Service Settings. New York: Springer; 2009.

42. Broadstock M, Michie S, Gray J, et al. The psychological consequences of offering mutation searching in the family for those at risk of hereditary breast and ovarian cancer--a pilot study. *Psychooncology*. 2000;**9**:537-48.

Table 1
Description of Phase II Participants Characteristics (N=712)

Variables in GPRI*		
Age in years: mean (SD)		49.80 (+12.53), range 18-80, median 50.00
Gender: n (%)	Male Female	85 (12%) 627 (88%)
Type of AOHD being tested: n (%)	Cancer (BRCA) Cancer (other, ie, Colon) Huntington disease Hemochromatosis	580 (82%) 90 (13%) 31 (4%) 5 (1%)
Personal history of disease being tested: n (%)		441 (62%)
Recent significant event (diagnosis of or loss of significant others to the disease being tested): n (%)		333 (47%)
Disease worries affect daily mood (strongly agree or somewhat agree): n (%)		189 (27%)
Sad in the past month (often or almost all the time): n (%)		121 (17%)
Anxious in the past month (often or almost all the time) n (%)		121 (17%)

* Note: there are missing data for some GRPT variables. The total count for each variable do not necessarily add up to 712

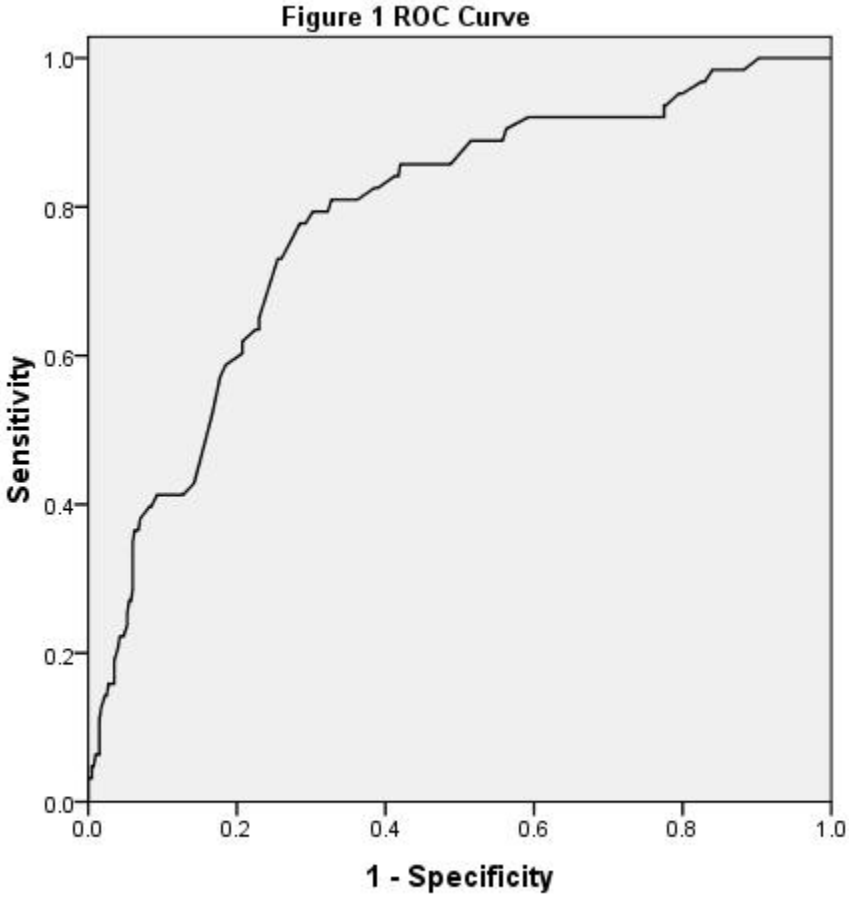
Table 2
Psychosocial Well Being 1 Month Post Genetic Testing Results By Disease Type (N=473)

	Overall N (%)	Huntington	*BRCA*	Other Cancer
IES intrusion >=17[a]	60 (13.0%)	5 (23.8%)	51 (12.5%)	4 (9.5%)
IES avoidance >=17[a]	65 (13.7%)	5 (23.8%)	57 (14.0%)	3 (7.1%)
BSI-18 total >=13[b]	95 (20.1%)	6 (28.6%)	86 (21.1%)	3 (7.1%)

a. Shemesh E. et al (2004) Posttraumatic stress, non adherence, and adverse outcome in survivors of a myocardial infarction. Psychosomatic Medicine, 66: 521-526
b. Zabora et al (2001): A new psychosocial screening instrument for use with cancer patients. Psychosomatics, 42:241–246

Table 3
GPRI Factor Solutions and Factor Loadings

	Factor Loadings	Commu-nalities	Item-Total	Item Mean
• My worries about the disease affect my daily mood	.759	.652	.582	2.22
• I worry often about my risk of getting the disease	.742	.551	.529	2.67
• I am concerned about my risk of getting the disease	.656	.484	.472	3.28
• I have generally felt nervous and anxious in the past month	.652	.538	.600	2.54
• I have generally felt sad in the past month	.627	.524	.572	2.58
• If I learn that I have a genetic mutation, … I will have more problems in my life	.617	.406	.399	2.79
…I will have difficulties with my family relationships	.513	.324	.424	1.62
… I will change plans for my career	.451	.228	.262	2.08
• The disease is currently causing a significant disruption in my family life	.568	.408	.463	2.42
• I am worried that my test result will impact on my relationship with my significant other	.546	.308	.383	2.54
• I am worried about talking to my children about the heritable nature of the disease for which I am being tested	.522	.326	.453	2.04
• I feel guilty that I might pass on the disease risk to my children	.508	.276	.414	3.11
Factor 1: Anticipated or experienced impact of having a disease risk or genetic mutation: 12 statements, Cronbach's alpha = .85, inter – item correlation = .32, variance explained = 22%				
• I have had emotional problems in the past	.796	.655	.423	2.66
• I have been diagnosed with a depressive or anxiety disorder in the past	.769	.596	.349	2.01
• I have had counselling with a mental health professional in the past	.762	.593	.433	2.85
• I have had emotional problems that led me to thoughts about suicide	.623	.389	.262	1.45
• I am now seeing a counselor for one or more of these emotional concerns	.509	.272	.274	1.35
Factor 2: Personal history or vulnerability to mental health issues or symptoms: 5 items, Cronbach's alpha = .76, inter – item correlation = .39, variance explained = 14%				
• I have taken care of a very ill parent or another close family member	.687	.493	.116	2.36
• I lost a close family member (e.g. parent/ sibling) to the disease for which I am receiving counseling/testing	.667	.445	-.002	2.87
• I have/had a personal diagnosis of the disease for which I am receiving counseling/testing	-.642	.413	-.073	3.47
Factor 3: Personal or family history of the genetic disease being tested in the clinic: 3 items, Cronbach's alpha = .08, inter – item correlation = .03, variance explained = 8%				



Genetic Psychosocial Risk Instrument (GPRI)

The purpose of this questionnaire is to help identify individuals who may need additional support while going through genetic testing. The questions are about your life experiences and feelings about the disease for which you are receiving genetic testing/counseling. Please note that whenever the word "disease" is used, it is referring to the disease for which you are having genetic testing and/or counseling. Please read each statement carefully, then respond by placing a firm checkmark in the most appropriate space.

Name:	Date (dd / mm / yyyy):

1. I have/had a personal diagnosis of the disease for which I am receiving counseling/testing (5) Yes (1) No
2. I have taken care of a very ill parent or another close family member (e.g. sibling) (0) Yes (1) No
   If yes, the illness was related to the condition for which I am receiving counseling/testing (5) Yes (3) No
3. I lost a close family member (e.g. parent/sibling) to the disease for which I am receiving counseling/testing (5) Yes (1) No
   If yes, please indicate who the family member was who died (check all that apply):
   (0) a parent (0) a sibling (0) other (specify)_____

	Strongly agree	Somewhat agree	Neither agree/disagree	Somewhat disagree	Strongly disagree	Not applicable
4. If I learn that I have a genetic mutation, I believe that:						
a. I will have more problems in my life	5	4	3	2	1	0
b. I will change plans for my career/ profession	5	4	3	2	1	3
c. I will have difficulties in my family relationships	5	4	3	2	1	3
5. The disease for which I am at risk is currently causing a significant disruption in my family life	5	4	3	2	1	3
6. I am worried that my test result will impact on my relationship with my significant other (or future partner)	5	4	3	2	1	3
7. I am worried about talking to my children (young or adult) about the heritable nature of the disease for which I'm being tested	5	4	3	2	1	3
8. My worries about the disease affect my daily mood	5	4	3	2	1	3
9. I worry often about my risk of getting the disease	5	4	3	2	1	3
10. I am concerned about my risk of getting the disease	5	4	3	2	1	3
11. I feel guilty that I might pass on the disease risk to my children	5	4	3	2	1	3

	Almost all of the time	Often	Sometimes	Hardly ever	Not at all
12. I have generally felt sad in the past month	5	4	3	2	1
13. I have generally felt nervous and anxious in the past month	5	4	3	2	1

14. I have had emotional problems in the past (5) Yes (1) No
15. I have had counseling with a counselor and/or a mental health professional in the past (5) Yes (1) No
16. I have been diagnosed with a depressive or anxiety disorder in the past (5) Yes (1) No
17. I have had emotional problems that led me to have thoughts about suicide (5) Yes (1) No
18. I am now seeing a counselor for one or more of these emotional concerns (5) Yes (1) No

19. I am interested in talking with a counsellor about one or more of these concerns (0) Yes (0)No

FOR OFFICE USE ONLY
Instruction to the user: Please sum the score of all items and enter the total score here _____
If the total score is 50 or greater, and if item 19 above is Yes, then a psychosocial referral is recommended.

Developing A Brief Screening Instrument for Psychosocial Risk Associated with Genetic Testing – A Pan Canadian Cohort Study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-002227.R1
Article Type:	Research
Date Submitted by the Author:	17-Jan-2013
Complete List of Authors:	Esplen, Mary Jane; Toronto General Hospital, Behavioural Science & Health Research Division; de Souza Institute, Cappelli, Mario; Children's Hospital of Eastern Ontario, ; University of Ottawa, Wong, Jiahui; de Souza Institute, ; University of Toronto, Department of Psychiatry Bottorff, Joan; University of British Columbia Okanagan, Hunter, Jon; Mount Sinai Hospital, ; University of Toronto, Department of Psychiatry Carroll, June; Mount Sinai Hospital, Dorval, Michel; Laval University, Wilson, Brenda; University of Ottawa, Allanson, Judith; Childrens Hospital of Eastern Ontario, Genetics Semotiuk, Kara; Mount Sinai Hospital, Zane Cohen Centre for Digestive Diseases Aronson, Melyssa; Mount Sinai Hospital, Zane Cohen Centre for Digestive Diseases Bordeleau, Louise; McMaster University, Charlemagne, Nicole; Toronto General Hospital, Behavioural Science & Health Research Division Meschino, Wendy; North York General Hospital,
Primary Subject Heading:	Genetics and genomics
Secondary Subject Heading:	Health services research
Keywords:	Genetics < TROPICAL MEDICINE, Cancer, Psychosocial, Screening, Psychosocial adjustment, behavioural science

Title

Developing A Brief Screening Instrument for Psychosocial Risk Associated with Genetic Testing – A Pan Canadian Cohort Study

Corresponding Author Address

Mary Jane Esplen, PhD
CIHR Scientist and Professor
Department of Psychiatry, Faculty of Medicine, University of Toronto
Behavioral Sciences and Health Research Division
University Health Network
200 Elizabeth Street, 9-EN-242A
Toronto ON M5G 2C4 Canada
Tel: (416) 340-3024
Fax: (416) 340-4739
Email: mesplen@uhnres.utoronto.ca

List of Authors and Institutions

Mary Jane Esplen PhD[1,2,3], Mario Cappelli PhD[4], Jiahui Wong PhD[2,3], Joan Bottorff PhD[5], Jon Hunter MD[2,6], June Carroll MD[6], Michel Dorval PhD[7], Brenda Wilson PhD[8], Judith Allanson MD[9], Kara Semotiuk MSc[10], Melyssa Aronson MSc[10], Louise Bordeleau MD[11], Nicole Charlemagne MSW[1], Wendy Meschino MD[12]

[1]University Health Network, Toronto ON; [2]University of Toronto: Department of Psychiatry, Toronto ON; [3]de Souza Institute, Toronto ON; [4]Children's Hospital of Eastern Ontario, Ottawa ON; [5]University of British Columbia Okanagan, Kelowna BC; [6]Mount Sinai Hospital, Toronto ON; [7]Laval University, Quebec QC; [8]University of Ottawa, Ottawa ON; [9]Eastern Ontario Regional Genetics Centre, Ottawa ON; [10]Zane Cohen Centre for Digestive Diseases, Mount Sinai Hospital, Toronto ON; [11]McMaster University, Hamilton ON; [12]North York General Hospital, Toronto ON.

Keywords:

Genetics, Psychosocial, Screening, Psychosocial Problems, Psychosocial Functioning, Psychological Risk Factors

Word Count: 5115

Abstract:

Objectives: To develop a brief, reliable and valid instrument to screen psychosocial risk among those who are undergoing genetic testing for Adult-Onset Hereditary Disease (AOHD).

Design: A prospective two-phase cohort study.

Setting: 5 genetic testing centres for AOHD such as cancer, Huntingtons, or Hemochromatosis, in ambulatory clinics of tertiary hospitals across Canada.

Participants: 141 individuals undergoing genetic testing were approached and consented to the instrument development phase of the study (Phase I). The Genetic Psychosocial Risk Instrument (GPRI) developed in Phase I was tested in Phase II for item refinement and validation. A separate cohort of 722 individuals consented to the study, 712 completed the baseline package, and 463 completed all follow-up assessments. Most participants were female, at mid-life stage. Individuals in advanced stages of the illness or with cognitive impairment or language barrier were excluded.

Interventions: Phase I: GPRI items were generated from 1) a review of the literature, 2) input from genetic counselors and 3) phase I participants. Phase II: further item refinement and validation was conducted with a second cohort of participants who completed the GPRI at baseline and were followed for psychological distress one month post genetic testing results.

Primary and secondary outcome measures: GPRI, Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), Brief Symptom Inventory (BSI), and Impact of Event Scale (IES).

Results: The final 20 item GPRI had a high reliability - Cronbach's Alpha at 0.81. The construct validity was supported by high correlations between GPRI and BSI and IES. The predictive value was demonstrated by a Receiver Operating Characteristic (ROC) curve of 0.78 plotting GPRI against follow-up assessments using HAM-D and HAM-A.

Conclusions: With a cut off score of 50, GPRI identified 84% of participants who displayed distress post genetic testing results, supporting its potential usefulness in a clinical setting.

Word count: 299
Trial registration: Not applicable

Summary

1) Article Focus

- A significant group of individuals undergoing genetic testing for Adult onset disease experience distress or challenges in adaptation, some might develop depression or anxiety
- Existing psychological screening tools do not take into consideration "risk factors" associated with heritable illness or genetic-related stressors
- A screening tool designed for genetic testing services is a useful tool to guide clinicians in relation to which patients would benefit from added psychosocial support during the genetic testing process.

2) Key Messages

- A subgroup of patients undergoing genetic testing required added psychosocial support to facilitate adaptation to genetic/ risk information. Busy genetic service providers can face challenges to identify these individuals and provide timely interventions or referrals.
- A new brief instrument was designed and validated to identify those individuals at risk for psychological distress such as depression or anxiety who are undergoing genetic testing for adult onset diseases.
- This is the first study to develop and validate a psychological screening instrument for genetic testing field.

3) Strengths and Limitations

- This newly developed tool, Genetic Psychosocial Risk Instrument (GPRI), is the first reported psychosocial screening instrument for use across Adult Onset Hereditary Diseases.
- The GPRI demonstrates promising psychometric properties as a tool designed to assist genetics health care providers determine which of their patients undergoing genetic testing for AOHD is at increased psychological risk and who will benefit from added psychosocial support.
- Study findings are limited by the characteristics of the sample, most participants were female and undergoing testing for BRCA1/2. Future studies could further address the validity of GPRI in male populations and in the rare adult onset hereditary diseases, such as Huntington's disease.

INTRODUCTION

Genetic predisposition is an important determinant of chronic disease and disability. Despite the benefits of genetic testing, such as increased screening or prophylactic interventions, individuals at high risk for serious illness may become increasingly fearful or distressed about the future. In fact, a consistent finding is that the majority of individuals do adjust to genetic test results, however a subset of individuals undergoing genetic testing for Adult Onset Hereditary Disease (AOHD) experience psychological distress, such as anxiety or depressive symptoms. A screening tool, designed for the genetic testing context, would be helpful in assisting geneticists, genetic counselors or primary care providers to identify this particular group for the implementation of at appropriate preventive or follow-up interventions. Herein, we present a newly developed psychological risk screening instrument that can be readily used within a genetic service for AOHD.

Risk Factors and Psychological Impact of Genetic Testing: The Evidence

The knowledge of genetic risk is life-long and individuals and families often find themselves confronted with ongoing need to face issues and make decisions. Examples include decision-making around prevention and treatment options (e.g. increased surveillance, prophylactic surgery, chemoprevention), the need to notify family members, and in relation personal decisions, such as those involving childbearing [1, 2]. Studies utilizing standardized measures of distress (e.g. symptoms of anxiety or depression) have demonstrated that 8 to 25% of individuals undergoing genetic testing experience distress, the level of which falls within the clinical ranges for depression and anxiety [2-5]. Studies that have utilized standardized disease specific measures of distress (i.e. instruments measuring breast/ovarian cancer worry) have demonstrated

higher prevalence levels [6, 7].

The risk factors for psychological symptoms amongst individuals undergoing genetic testing have been delineated in several studies [4, 8, 9]. While there is generally elevated distress using global measures for depression or anxiety among those who receive positive test results [9-11], individuals testing negative or receiving uninformative results may also have adjustment difficulties [12]. For example, individuals may feel guilt or continue to worry about their disease risk [2, 7, 12]. These findings highlight the importance of considering risk factors in addition to the test result itself. Individuals who have elevated psychological symptoms at the pre-test stage and those with a previous psychiatric history (i.e., depression) are particularly at risk for an adverse psychological outcome after testing [2, 8, 9].

Additional risk factors for distress are more specific to the genetics context and include the level of penetrance of the gene mutation or degree of certainty of developing the disease [4]. The perception of control over the disease (including the number of prevention/treatment options) and perception of the immediacy of risk (proximity in age to perceived disease onset) are important predictors [4, 13]. The expectation of a negative test result can play a role in adjustment, as can the context of test results of other family members [9, 14]. As in other medical areas, specific coping styles can affect adjustment [15]. The prior experiences with loss of family members to disease, as well as the developmental level (i.e. young age) of the individual at the time of the loss [2, 3, 16] are significant factors affecting potential adjustment. In addition, the prior experience of giving care to a family member with the disease and lower levels of social support have been associated with poorer adjustment following a positive test result [2-4, 8, 16].

It is clear that there is not one predominant factor, but rather, a series of variables that may contribute to elevated levels of psychological distress [2, 17]. Emotional reactions may impede the assimilation of risk information and the adoption of preventive measures [2, 18]. Psychological distress occurs along a continuum [19, 20] and can be difficult to identify by health professionals [21]. Distress may not become manifest to the health care team until the patient reaches an observable crisis level, i.e. the onset of severe depression or anxiety, or significant conflicts with the family. An early screening instrument would enable healthcare providers to identify patients being at higher psychological risk in order that appropriate support can be given at the right time. In fact, there is now a general consensus that genetic testing should be accompanied by psychological support to promote optimal adjustment [2, 22].

Screening for Psychological Risk Factors- Why is it necessary?

The gold standard for identifying psychologically distressed individuals involves structured clinical interviews administered by a clinical psychologist or psychiatrist [21]. However, it is too costly and often not feasible in genetic clinics. Standardized measures of psychological functioning (e.g. global scales of depression or anxiety) can also be used as a method for identifying distress. However, few clinics use these measures in practice because of personnel and time requirements for scoring and interpretation of them. Furthermore, these instruments tend to identify global symptoms that are consistent with the diagnostic classifications of anxiety and/or depression and may lack sensitivity to the important and unique issues that surround genetic testing; issues that may include concerns about family members, past experiences with an inheritable disease, and uncertainty about risk reduction options [19, 21]. In addition, items on these measures typically focus on symptoms of anxiety or depression, rather on variables

associated with heritable disease or genetic testing or risk, which may pose barriers for use by genetics health service providers who may prefer instruments that, at face value, appear to them and their patients as being clinically more relevant to the genetic testing context.

More recently, new outcome measures designed to assess the psychological impact of receiving genetic information have been developed. For example, the Multidimensional Impact of Cancer Risk Assessment (MICRA) is designed to assess concerns and impacts associated with genetic testing for BRCA1/2 [19] and another tool, the Psychological Adaptation to Genetic Information Scale, is now available [23]. While these measures will require further validation they provide more clinically relevant approaches to capturing specific impacts of genetic information, such as the increased sense of vulnerability often experienced following genetic testing [19, 23].

Measures of global psychological functioning and the evolving outcome measurement tools for the genetics field are not designed to "predict" vulnerability for future distress, but rather, measure current distress levels. Screening, the aim of the tool developed in this study in contrast, is a rapid, cost-effective alternative [21] to prospectively identify individuals who may experience significant difficulty in their attempts to adapt to their genetic information [17]. A screening tool enables providers to offer timely and focused educational and psychosocial interventions to *prevent* future distress.

The primary *objective* of this study was to develop a brief, reliable and valid psychological risk screening instrument for use in the genetic testing context. The new instrument aimed to incorporate empirically based risk factors for psychological symptoms and would need to show a high sensitivity, specificity and predictive validity indicating risk for future distress post genetic testing results. A cutoff point would need to be determined to guide

clinical decisions as to whether or not to refer, further assess, or intervene to reduce an individual's expressed concern.

METHODS AND MATERIALS

The study was carried out from September 2005 to July 2010, with research ethics board approval from participating genetics clinics: Toronto (Mount Sinai Hospital, North York General Hospital, Princess Margaret Hospital); Ottawa (Children's Hospital of Eastern Ontario); and Vancouver (British Columbia Cancer Agency). Individuals beginning the genetic testing process for AOHD at each site were approached by genetic counsellors on the project team for their permission to be contacted about the study. Those who expressed interest were mailed the baseline package that included the informed consent. The informed consent included all components of the study, including questionnaires, follow-up phone calls, telephone interviews, as well as to the release of their genetic testing information to the research team.

A two phase approach was used for this study**: *Phase I:*** *Item Generation and Refinement,* and ***Phase II:*** *Validation*. The multi-stage method [24] takes validation into consideration at each stage of scale development and has been used successfully in previous studies [25].

Phase I: Item Generation and Refinement.

Item generation

To generate items for the Genetic Psychosocial Risk Instrument (GPRI), a literature search was performed for the following AOHDs: Cancer (Hereditary Breast-Ovarian Cancer Syndrome/ Lynch Syndrome), Huntington Disease (HD), and Hemochromatosis. These diseases were selected as they represented the majority of patients attending genetic clinics and had an

associated available psychosocial literature for review. Databases including Cinahl (1982 to 2006), Medline (1966 to 2006), PsychInfo (1985 to 2006), and Pubmed (1985 to 2006) were searched as well as hand search of references from major publications. Keywords included: genetic screening, genetic testing, psychological, psychological well-being, psychological adjustment, stress, adaptation, cancer worry, disease worry, and distress. Selection criteria for the literature review included studies with a follow-up design or review articles. Each selected study was reviewed by two reviewers on its quality of evidence and generalizability using a standardized template. A total of 73 relevant studies were identified among the disease groups: 49 on cancer, 20 on HD, 2 on Hemochromatosis, and 2 described mixed conditions.

Risk factors for psychological distress identified by the literature review provided the basis for item generation. Items were written in a mixed format where respondents were asked for their endorsement of each statement ranging from Yes/No for risk factors of binary nature, to a 5-point likert-type scale for risk factors with stages in frequency and/or intensity. The instrument items were further refined by 10 genetic service providers (3 geneticists, 4 genetic counselors, 2 oncologists, 1 genetics nurse) rating items on *comprehension, readability, and perceived clinical relevance* using a ten-point scale with 0 being "excellent/definitely relevant" and 10 being "very poor/definitely not relevant". Risk factor items were removed if rated above five by more than 3 providers. Providers were also asked to suggest additional risk factor items. These suggestions were checked against the literature for empirical evidence. Following this step, 7 volunteers undergoing genetic testing for AOHDs were recruited to try out the scale for clarity, succinctness and relevance from the clients' perspectives. At this stage, the proposed instrument consisted of 56 items: demographics (4 items); perceived risk (8 items); life events and family history of the disease (8 items); perceived impact of carrying a mutation (9 items);

family communication (6 items); disease specific concerns (5 items); optimism (3 items); social support (3 items), pre-morbid functioning and previous psychiatric history (10 items).

Item refinement:

Subjects: Following informed consent, a convenient sample of 141 participants who had given blood for genetic tests at the Toronto and Ottawa sites completed the GPRI (using a three patients per item ratio) to select the best items for the candidate scale. The participants were middle aged (48.67 ± 13.29), mostly female (77%) testing for hereditary breast cancer, and many (65%) had already suffered the onset of the illness.

Scoring: To ensure that binary items carry an equal weight as the 5-point likert-type items, a score of 5 was assigned to *Yes* and 1 to *No.* A score of 3 or mean-substitute was assigned to *Not Applicable* to allow it to be counted in the total score. Reliability analysis was carried out and a Cronbach's Alpha was set for .75 or higher for the scale to move to the next phase [26]. Any item with an item-total correlation less than .20 was identified for potential removal. Using team consensus, a total of 19 items were removed, combined or substituted, resulting in a 37 item GPRI candidate scale at the end of phase I.

Phase II: Scale Validation

Subjects: Individuals undergoing genetic testing for one of the AOHDs in each of the five study sites were invited to participate: 1) age 18 or above undergoing genetic testing for cancer, HD, or Hemochromatosis; 2) fluent in English; and 3) residing within 1.5 hours driving distance from study site. Although the onset of an AOHD was not an exclusion criterion, individuals in advanced stages of the illness and / or who were unable to consent due to cognitive impairment

were excluded. At baseline, participants were asked to complete a set of self-report questionnaires (e.g. Brief Symptom Inventory, etc.) described below within a one month period following the provision of a blood sample. For those who received a genetic test result, questionnaires were mailed within two weeks to one month of the disclosure of test result. These participants were also telephoned to complete the Hamilton Depression and Hamilton telephone-based Anxiety Scales to further assess depressive and anxiety symptoms. .

Materials**:** At baseline, three psychosocial measures were used: *GPRI Candidate Scale* from Phase I. To facilitate scoring of the scale by genetic providers, scores for response to each item on the GPRI were imbedded in the questionnaire, where clinicians could calculate a total score in less than 5 minutes. *Brief Symptom Inventory* (BSI) The BSI is a 53-item measure of psychological distress that contains three global scales i) depression, ii) anxiety and iii) somatization [27]. It is widely used in medical and psychiatric populations to assess psychological functioning; *Impact of Event Scale (IES)*: The IES is a 15-item, likert-style scale used to assess the experience of a specific stress response and is designed to be easily anchored in relation to a specific stressor or life event. As previously utilized in the genetics literature to assess genetic testing-related distress, the IES items were anchored in relation to the event of "the genetic test result". The IES has two sub-scales: i) intrusive thoughts and feelings associated with the stressful life event, and ii) items associated with patterns of avoidance of certain thoughts, feelings, or situations [28].

Measures at one month post genetic testing results included: the self -reports scales of the BSI, IES and each participant received a telephone call for the telephone-based Hamilton Depression 29-item Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A). The HAM-D evaluates depressed mood, vegetative and cognitive symptoms of depression, and

comorbid anxiety symptoms [29]. The HAM-A quantifies the severity of anxiety symptomatology and consists of 14 items. The HAM-D and HAM-A have demonstrated validity in clinical interview, in person or by telephone [30]. These two instruments were selected as main outcome measures based on the literature that the standardized interview based-rating scales should be used over subjective report scales as the principal outcome criterion in psychological distress both in general practice and in research trials [34]. Cases would be defined by established cut-offs from the literature for HAM-D >=12 [35] or HAM-A >=10 [36]. These cut off points were established for populations in general practice, which was our study population.

The one-month follow-up time point was selected as it is when elevated distress might occur [31]. In addition, the 2-week duration criterion for depression defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) is met by this time frame.

Assessing Psychometric Property of the Scale

As a first step, items were required to have at least an 80% response rate. Second, each item was examined to determine its contribution to the internal consistency of the total 37-item scale. The minimum item-total correlation was set at .20 [32].

A principal components factor analysis with varimax rotation was performed on the candidate scale to examine the factor structure and the loading of the items. To assess the *convergent validity* of the candidate scale, the correlations between baseline GPRI, IES and BSI were calculated. To assess the *sensitivity, specificity and predictive value* of the GPRI, the follow-up HAM-D and HAM-A were used to identify "cases" who met cut offs for either the depression or anxiety symptomatology. For example, participants with a high GPRI at baseline

would be classified as "at risk" for future onset of adjustment difficulties. This would be confirmed by a high HAM-D or HAM-A score or "case" during 1 month follow-up. Similarly, those with a low GPRI score should receive low score in HAM-D or HAM-A as "non-cases". The predictive value of the GRPI, describing the number of test-positives (in our case, high GPRI) who truly have the psychological condition (i.e. cases identified by HAM-D or HAM-A), was tested by a Receiver Operating Characteristic (ROC) curve which visually plotted the true positive rate (sensitivity) over false positive rate (1-specificity). We included cases to be identified by either anxiety and/or depressive symptomatology as both have been reported in the literature [8, 9].

To address the issue of missing follow-up data in a cohort study, as suggested in the literature [33], we tested the assumption that the sub sample with missing data had a similar baseline exposure (similar GPRI) as the non-missing subsample by comparing baseline GPRI between the participants and dropouts. This step assesses if there was systematic bias resulting from the loss of information in the follow-up period.

RESULTS

Participant characteristics

Study packages were mailed to 1129 individuals interested in hearing more about the study. Of these individuals, 722 of them consented and 712 (98%) completed the GPRI. Most participants were tested for the inheritable cancers, while a small percentage of participants were tested for hemochromatosis and HD. Similar to phase I, phase II participants were mostly female, at mid-life stage, and more than half had a past diagnosis of the disease (see table 1).

Insert Table 1 about Here

Of the 712 participants, 85 (12%) did not receive genetic testing results at the scheduled follow-up time and were not eligible for follow-up measures on psychological symptoms in response to a genetic testing result. Of the remaining 627 participants, 152 (24%) did not return the self-administered follow-up questionnaires and 12 (2%) submitted the follow-up questionnaire package but did not complete a standardized telephone interview using HAM-D and HAM-A (up to 4 telephone calls were made to reach each participant). Therefore the final number of participants with complete follow-up data is 463 (74%). The age, and baseline GPRI score between individuals who did not receive genetic testing results (age 51.4±12.7, GPRI 49.3±12.7), those who did not return the follow-up questionnaires (age 48.1±11.6, GPRI 50.2±14.4) and those who completed follow-up measures (age 50.1±12.8, GPRI 49.1±13.5) were compared. There was no statistically significant group difference (ANOVA and all post-hoc comparisons $p>0.05$).

Because of the similarity between the dropouts and completers, we proceeded with reliability and validity analysis of the tool using the subsample that provided outcome data.

We carried out the calculations for distress level, for example, for depression and anxiety symptoms using the BSI data, for specific distress associated a genetic test result using the IES. Approximately, 13.0% to 20.1% of participants reached the threshold of moderate to severe distress respectively (see table 2).

Insert Table 2 about Here

HAM-D and HAM-A interview data from 463 participants were used as a further validation tool to measure psychological symptoms post genetic testing results. Defined by cut-offs for HAM-D >=12 [35] or HAM-A >=10 in the literature [36], the rates for psychological

distress of either depression or anxiety was 13.7% (N=63). The rate was 13% for HD, 15% for breast cancer and 7% for Lynch Syndrome.

Reliability and Factor Analysis

A reliability analysis was performed on 37 items. Twenty items belonging to 18 questions were selected based on the criteria for item selection described in the methods section. The Cronbach's alpha of the 20 item GPRI was 0.81 suggesting a good level of internal consistency.

The factor analysis resulted in a psychometrically sound 3-factor solution, with subscales representing the dimensions of: 1) *Perceived impact and personal adjustment to genetic testing* (12 items); 2) *Past history of mental health concerns* (5 items) and 3) *Personal history/family history/loss to cancer* (3 items). All three factors met the minimum Eigenvalue criteria of 1.

The first, 12-item factor (ALPHA = 0.85), accounting for 22% of the variance, includes items associated with the anticipated or experienced impact of being at high risk for AOHD. Example items included: "My worries about the disease affect my daily mood"; "The disease for which I am at risk is currently causing a significant disruption in my family life".

The second 5-item factor (ALPHA = 0.76), accounted for an additional 14% of the total variance, and reflected a sense of a person's past history or vulnerability in the area of mental health , e.g. "I have had emotional problems in the past", These items have been used in other medical health areas [37, 38] and tend to be predictive of maladjustment [20] following a life event.

The third 3 item factor (ALPHA = 0.08), accounted for 8% of the total variance and pertained to personal or family-related experiences associated with the hereditable disorder for which the participant is undergoing testing. . Examples include: "I have a personal diagnosis of

the disease for which I am receiving counseling"; "I lost a close family member to the disease for which I am receiving counseling"; and "I have taken care of a very ill parent or another close family member". These 3 final items had low item total correlation because they were different from the rest of the items in that they focused on direct experiences related to the illness, rather than psychosocial-related items. These items were kept in the scale as they contributed significantly to the overall variance, and correlated highly with HAM-D and HAM-A. To determine the relationships between the three factors/subscales, correlations were computed. Factor1 and factor2 had moderate correlations with each other (factor1/factor2 $r=0.30$, $p<0.01$). The correlation of the first two factors with factor3 was much lower as expected (factor1/factor3 $r=0.06$, and factor2/factor3 $r=0.01$, not statistically significant). These results support the multidimensional character of the GPRI scale (see Table 3).

Insert Table 3 about Here

One additional statement "I am interested in talking to a counselor about one or more of these concerns" was added to the tool at the end as suggested by participants and providers to remind them the option of seeing a counselor if required. This statement is not part of the items examined during the instrument development and therefore does not carry a score.

The total score for the 20 item GPRI ranged from 20 to 100, with a sample mean 49.36 ± 13.23. The total was calculated by the sum of the raw scores for each of the statements. Females had a significantly higher score for the GPRI than males (50.37 ± 13.14 vs. 41.91 ± 11.47, $p<0.01$), and participants testing for HD had a higher, but non-significant score than participants testing for cancer (52.24 ± 13.24 vs. 49.37 ± 13.22, n.s.).

Validity

Construct validity – correlations: The GPRI was assessed for its correlation with other standardized self-report measures of psychological functioning collected at baseline. Convergent validity was demonstrated by the correlation between the GPRI and the following measures: a positive correlation with the IES total score at r = .51, p< .001, and with BSI at r = .58, p< .001.

Sensitivity, specificity and the predictive value of GPRI for future distress: The telephone interview-based HAM-D and HAM-A were used to identify subjects who presented specific psychological symptoms of distress such as depression and/or anxiety during the one month post genetic testing follow-up. A total of 63 "cases" (13.6% of 463 completers) were identified as having psychological distress levels above specified thresholds defined in the methods section for either anxiety or depression symptoms or both. About 23% among participants testing positive met the distress threshold, as did 10% among those with negative results, and 20% among uninformative. Participants scoring above HAM-D (N=55) threshold had significantly higher GPRI scores than participants below the threshold (N=408) (61.12±13.27 vs. 47.91±12.27, p<0.01). Same patterns were observed for HAM-A high (N=40) vs. low (N=423) (62.53±12.92 vs. 48.25± 12.43, p<0.01).

Other demographic characteristics of these 63 subjects include: most were female and undergoing testing for BRCA1/2, which was similar to the whole sample of 712 (table 1). Compared with the whole sample, these subjects had a slightly higher percentage of personal history of cancer (65% vs. 62%), higher rate of recent significant event of loss (56% vs. 47%), greater percentage reporting disease worries affecting mood (54.8% vs. 27%), having a feeling of sadness in the past month (46% vs. 17%) and anxiousness in the past month (33% vs. 17%). Our instrument captured all of these characteristics of this subsample.

The predictive value of a test describes how many of the test-positives (in this case, a high score on GPRI) truly have the psychological condition. An ROC curve was used to plot the true positive rate (sensitivity) over the false positive rate (1-specificity). A good ROC curve rises sharply, indicating a high proportion in true positive and a low proportion of false positives. The ROC curve for the GPRI was 0.78, which is considered as an indicator of an adequate screening instrument [39].

An important purpose of the GRPI in our study was to identify individuals at risk for post genetic testing psychological distress. Therefore, the cutoff value was set to maximize sensitivity – in another word, not to miss detecting a "case". Using a GPRI cut off score of 50, the instrument was able to predict 84% of the "cases" identified by HAM-D or HAM-A conducted post genetic testing results, with a specificity value of 60% (Figure 1).

Insert Figure 1 about Here

DISCUSSION

The aim of this study was to develop a brief, easy-to-use psychosocial screening instrument specific for the genetic testing context and to examine its reliability and validity (Appendix A). To our knowledge this is the first report of a psychosocial screening instrument for use across AOHD. Unlike current psychological instruments used mainly in research studies in genetics clinics to identify existing global symptoms of depression and anxiety, or impacts, the GPRI assesses *psychological risk factors*, such as the specific anticipated impacts of a genetic testing result and the perception of the disease. The GPRI demonstrates promising psychometric properties as a tool designed to assist genetics health care providers determine which of their

patients undergoing genetic testing for AOHD is at increased psychological risk and should likely be considered for additional psychosocial support to facilitate adjustment to a test result.

A high reliability was demonstrated by a Cronbach's Alpha at 0.81, moderate to high item-total correlation and inter-item correlation of the whole scale. The construct validity of the scale was supported by high correlations between the GPRI and standardized psychological measures (BSI, IES). The clinical utility and predictive value of the GPRI was supported as well. A GPRI score above the cutoff of 50 at baseline was able to predict 84% of "distress" cases identified by HAM-D or HAM-A, a strong indicator of its potential usefulness in a clinical setting.

A brief self-administered screening tool will be easy and likely highly acceptable for incorporation into genetics clinics. The GPRI can be completed and scored quickly during clinical visits and without additional burden to patients and health providers. In addition, by focusing specifically on known risk factors associated with inheritable illness, the instrument will be perceived as being more clinically relevant and acceptable to patients. Patients with higher GPRI scores can be flagged and either receive telephone follow-up to further assess concerns or potential distress or be invited back for an appointment for further assessment and required psychological treatment.

Alternatively, genetic clinics with available psychosocial personnel could utilize the tool to guide referrals for a formal psychosocial assessment that can further explore and address specific self-reported psychological factors. For example, in the case where an individual is particularly fearful of developing an illness or is concerned about specific impacts, such as expecting relationship or family communications difficulties, information on communication strategies, personal coaching or family–based interventions could be employed to support the

individual. For an individuals who reports a past history of psychological illness, a mental health professional could further assess current psychological functioning and implement specific approaches, and could offer cognitive-behavioral strategies or psychotropic medication to assist in the management of anxiety or depressive symptoms [40]. Several items incorporate variables related to heritable disease experiences and associated perceptions which can be used to guide educational interventions to correct any myths or beliefs.

The scale appeared highly acceptable to patients. A high face validity will contribute to better scale uptake being perceived as "user friendly" and clinically relevant, compared for example, to a standardized psychological instrument on depression, which have demonstrated some barriers to clinic uptake [19]. The GPRI in contrast might be considered as a "communimetric measure", that is, the items themselves are useful for the clinician in communicating concerns about specific areas of functioning directly with the patient [41].

Left untreated, significant levels of psychological symptoms may lead to lower quality of life [40], and lower satisfaction with genetics services [21]. A psychological screening approach allows both for careful monitoring during a known stressful period-that of awaiting test results [42], and provides an opportunity for any planned follow-up care. Flagging those individuals who might benefit most from psychosocial care also best utilizes the often limited psychological resources in genetic clinics [2, 20, 21].

Our study findings are limited by the characteristics of the sample, in that most participants were female and undergoing testing for *BRCA1/2*. This pattern is similar to that observed in the literature on genetic testing for AOHD, which is predominantly focused on Hereditary Breast-Ovarian Cancer Syndrome. We attempted to obtain a larger sample of individuals undergoing genetic testing for HD or Lynch Syndrome which would presumably

provide a greater sample of males. However, these sample pools were much smaller. However, this study and the resulting GPRI represent an attempt to begin the development of a general tool that addresses concerns that are relevant across genetic samples. Our belief stemming from clinical practice and the associated literature suggest that the identified mental health issues or adjustment risk factors are not disease specific. We suggest that future studies further address the validity of GPRI in male populations and in the rare adult onset hereditary diseases, such as HD. Future studies should also include randomized controlled trials to assess the effectiveness of the GPRI in predicting distress, its impact on referral patterns, patient and provider satisfaction, as well as on cost-effectiveness. The GPRI could also be evaluated in primary care settings where genetics services might be offered more frequently to meet the demand.

CONCLUSIONS

This is the first study to develop a screening tool specifically to help identify individuals undergoing genetic testing for AOHD who are at increased psychological risk. The study resulted in an easy to use, 20-item scale consisting of 3 factors with promising psychometric properties. The GPRI has the potential to be used as a clinical screening tool and as a validated measure for future studies. Future work can examine its impact on clinical referral patterns within the field of genetics, and on its acceptability, reliability and validity with larger samples of individuals undergoing genetic testing for HD, Lynch Syndrome, and potentially for emerging new genetic tests, such as for cardiac or psychiatric disorders.

Acknowledgement

The first author is a recipient of a career scientist award from the Canadian Institutes of Health Research (CIHR) and the Ontario Women's Health Council. This study was funded by Canadian Institutes of Health Research (CIHR) Grant No. AHC 73144. We would like to express our gratitude to all the genetic testing patients who participated in our study. Thank you for your contribution towards this very important work and the development of the instrument. Thank you also to the genetic counselors and clinic staff from the participating genetic centers who assisted in recruitment: Children's Hospital of Eastern Ontario (Eastern Ontario Regional Genetics Centre); North York General Hospital (Clinical Genetics); Mount Sinai Hospital (Familial GI Cancer Registry & Familial Breast Cancer Clinic); Princess Margaret Hospital (Familial Breast & Ovarian Cancer Clinic); and BC Cancer Agency (Hereditary Cancer Program). We would also like to thank the research staff for their commitment and hard work to complete this national multi-site study. Finally, the team would like to pay special recognition to the late Dr. Anne Summers, who was co-investigator on the team. Her dedication to the need for empirically based tools and her strong vision to support recipients of new genetic technology were key influences in the conceptualization, funding and completion of this study.

Ethics: Research Ethics Board approval was obtained at all five participating sites: Toronto (Mount Sinai Hospital, North York General Hospital, Princess Margaret Hospital); Ottawa (Children's Hospital of Eastern Ontario); and Vancouver (British Columbia Cancer Agency).

Data Sharing Statement: There is no additional data available

Conflict of Interest: The authors do not have any conflict of interest to disclose.

Funding: This study was funded by Canadian Institutes of Health Research (CIHR) Grant No. AHC 73144.

Contributorship Statements

Dr. Mary Jane Esplen

Principal Applicant responsible for leading all aspects of the research, oversees budget, hiring staff, supervising data collection, analysis and interpretation, and writing of all manuscripts and reports.

Dr. Mario Cappelli

Co-principal inv. responsible for assisting in item generation and refinement, the implementation of data collection, interpretation of findings and writing of manuscripts and reports.

Dr. Jiahui Wong

Co- Applicant responsible assisting in instrument development, statistical procedures, sampling and interpretation of findings and writing of manuscripts and reports.

Dr. Joan Bottorff

Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services, development of guidelines and writing of manuscripts and reports.

Dr. Jon Hunter

Co-Applicant responsible for assisting in item generation and refinement, guideline development, interpretation of findings and writing of manuscripts and reports.

Dr. June Carroll

Co-Applicant responsible for assisting in item generation and refinement, implementation of the screening validation strategy and development of guidelines, interpretation of findings and writing of manuscripts and reports.

Dr. Michel Dorval

Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services, interpretation of findings and writing of manuscripts and reports.

Dr. Brenda Wilson

Co-Applicant responsible for co-leading the implementation of the consensus guidelines components of the proposed study. Will assist in item generation for tool, interpretation of findings, writing of manuscripts and reports.

Dr. Judith Allanson

Co-Applicant responsible for refining of items, guiding the recruitment of providers/patients and testing of the instrument in genetic services, development of guidelines and writing of manuscripts and reports.

Ms. Kara Semotiuk

Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services and development of guidelines, and writing of manuscripts and reports.

Ms. Melyssa Aronson

Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services, development of guidelines and writing of manuscripts and reports.

Dr. Louise Bordeleau

Co-Applicant responsible for overseeing recruitment at MSH and UHN site in Toronto, testing of instrument and interpretation of findings, writing of manuscripts and reports.

Ms. Nicole Charlemagne

Project coordinator, responsible for: patient recruitment and follow-up; assisting in item generation, refinement, and overall layout and design of tool; data collection, data entry, and data clean-up; revisions and submission of manuscript.

Dr. Wendy Meschino

Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services, interpretation of findings and writing of manuscripts and reports.

REFERENCES

1. Lerman C, Croyle RT. Emotional and behavioral responses to genetic testing for susceptibility to cancer. *Oncology (Williston Park)*. 1996;**10**:191-5, 9; discussion 200-2.

2. Bleiker EM, Hahn DE, Aaronson NK. Psychosocial issues in cancer genetics--current status and future directions. *Acta Oncol*. 2003;**42**:276-86.

3. Wellisch DK, Lindberg NM. A psychological profile of depressed and nondepressed women at high risk for breast cancer. *Psychosomatics*. 2001;**42**:330-6.

4. Broadstock M, Michie S, Marteau T. Psychological consequences of predictive genetic testing: a systematic review. *Eur J Hum Genet*. 2000;**8**:731-8.

5. Ho SM, Ho JW, Bonanno GA, et al. Hopefulness predicts resilience after hereditary colorectal cancer genetic testing: a prospective outcome trajectories study. *BMC Cancer*. 2010;**10**:279.

6. Trask PC, Paterson AG, Wang C, et al. Cancer-specific worry interference in women attending a breast and ovarian cancer risk evaluation program: impact on emotional distress and health functioning. *Psychooncology*. 2001;**10**:349-60.

7. Coyne JC, Kruus L, Racioppo M, et al. What do ratings of cancer-specific distress mean among women at high risk of breast and ovarian cancer? *Am J Med Genet A*. 2003;**116A**:222-8.

8. Marteau TM, Croyle RT. The new genetics. Psychological responses to genetic testing. *BMJ*. 1998;**316**:693-6.

9. Meiser B. Psychological impact of genetic testing for cancer susceptibility: an update of the literature. *Psychooncology*. 2005;**14**:1060-74.

10. Hamilton JG, Lobel M, Moyer A. Emotional distress following genetic testing for hereditary breast and ovarian cancer: a meta-analytic review. *Health Psychol*. 2009;**28**:510-8.

11. Shaw C, Abrams K, Marteau TM. Psychological impact of predicting individuals' risks of illness: a systematic review. *Soc Sci Med*. 1999;**49**:1571-98.

12. Dorval M, Gauthier G, Maunsell E, et al. No evidence of false reassurance among women with an inconclusive BRCA1/2 genetic test result. *Cancer Epidemiol Biomarkers Prev*. 2005;**14**:2862-7.

13. Cameron LD, Sherman KA, Marteau TM, et al. Impact of genetic risk information and type of disease on perceived risk, anticipated affect, and expected consequences of genetic tests. *Health Psychol*. 2009;**28**:307-16.

14. Smith KR, West JA, Croyle RT, et al. Familial context of genetic testing for cancer susceptibility: moderating effect of siblings' test results on psychological distress one to two weeks after BRCA1 mutation testing. *Cancer Epidemiol Biomarkers Prev*. 1999;**8**:385-92.

15. Dougall AL, Smith AW, Somers TJ, et al. Coping with genetic testing for breast cancer susceptibility. *Psychosom Med*. 2009;**71**:98-105.

16. Esplen MJ, Urquhart C, Butler K, et al. The experience of loss and anticipation of distress in colorectal cancer patients undergoing genetic testing. *J Psychosom Res*. 2003;**55**:427-35.

17. Zabora JR. Screening procedures for psychological distress. In: Holland JC, editor. Psycho-Oncology. New York: Oxford University Press; 1998. p. 653-62.

18. Watson M, Lloyd S, Davidson J, et al. The impact of genetic counselling on risk perception and mental health in women with a family history of breast cancer. *Br J Cancer*. 1999;**79**:868-74.

19. Cella D, Hughes C, Peterman A, et al. A brief assessment of concerns associated with genetic testing for cancer: the Multidimensional Impact of Cancer Risk Assessment (MICRA) questionnaire. *Health Psychol*. 2002;**21**:564-72.

20. Zabora J, BrintzenhofeSzoc K, Curbow B, et al. The prevalence of psychological distress by cancer site. *Psychooncology*. 2001;**10**:19-28.

21. Thewes B, Meiser B, Tucker K, et al. Screening for psychological distress and vulnerability factors in women at increased risk for breast cancer: A review of the literature. *Psychology, Health & Medicine*. 2003;**8**:289-303.

22. Howell D, Keller-Olaman S, Oliver T, et al. A Pan-Canadian Practice Guideline: Screening, Assessment and Care of Psychosocial Distress (Depression, Anxiety) in Adults with

Cancer. Toronto: Canadian Partnership Against Cancer (Cancer Journey Action Group) and the Canadian Association of Psychosocial Oncology2010.

23. Read CY, Perry DJ, Duffy ME. Design and psychometric evaluation of the Psychological Adaptation to Genetic Information Scale. *J Nurs Scholarsh*. 2005;**37**:203-8.

24. Jackson D. A sequential system for personality scale development. In: Spielberger C, editor. Current Topics in Clinical and Community Psychology. New York: Academic Press; 1970. p. 61-96.

25. Stuckless N, Goranson R. The vengeance scale: Development of a measure of attitudes toward revenge. *Journal of Social Behavior and Personality*. 1992;**7**:25-42.

26. Briggs SR, Cheek JM. The role of factor analysis in the development and evaluation of personality scales. *Journal of Personality*. 1986;**54**:106-48.

27. Derogatis LR. The brief symptom inventory (BSI). Administration, Scoring and Procedures Manual. 3rd ed. New York: National Computer Systems; 1993.

28. Horowitz MJ, Wilner N, Alvarez W. Impact of Events Scale: A Measure of Subjective Stress. *Psychosomatic Medicine*. 1979;**41**:209-18.

29. Hamilton MA. A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*. 1960;**23**:56-23.

30. Katzelnick DJ, Simon GE, Pearson SD, et al. Randomized trial of a depression management program in high utilizers of medical care. *Arch Fam Med*. 2000;**9**:345-51.

31. DudokdeWit AC, Tibben A, Duivenvoorden HJ, et al. Predicting adaptation to presymptomatic DNA testing for late onset disorders: who will experience distress? Rotterdam Leiden Genetics Workgroup. *J Med Genet*. 1998;**35**:745-54.

32. Walsh W, Betz N. Tests and Assessments. New Jersey: Prentice Hall Inc; 1985.

33. Melnick EL, Everitt BS. Quantitative risk analysis and assessment. Hebokea NJ: John Wiley & Sons; 2008.

34. Moller HJ. Rating depressed patients: observer- vs self-assessment. *Eur Psychiatry*. 2000;**15**:160-72.

35. Aben I, Verhey F, Lousberg R, et al. Validity of the beck depression inventory, hospital anxiety and depression scale, SCL-90, and hamilton depression rating scale as screening instruments for depression in stroke patients. *Psychosomatics*. 2002;**43**:386-93.

36. Pasquini M, Biondi M, Costantini A, et al. Detection and treatment of depressive and anxiety disorders among cancer patients: feasibility and preliminary findings from a liaison service in an oncology division. *Depress Anxiety*. 2006;**23**:441-8.

37. Beck CT. A checklist to identify women at risk for developing postpartum depression. *J Obstet Gynecol Neonatal Nurs*. 1998;**27**:39-46.

38. Reid AJ, Biringer A, Carroll JD, et al. Using the ALPHA form in practice to assess antenatal psychosocial health. Antenatal Psychosocial Health Assessment. *CMAJ*. 1998;**159**:677-84.

39. Goutham R. What is an ROC curve? *The Journal of Family Practice*. 2003;**52**:695.

40. Esplen MJ, Hunter J. Therapy in the Setting of Genetic Predisposition to Cancer' in 'Handbook of Psychotherapy in Cancer Care. In: Watson M, Kissane D, editors. Handbook of Psychotherapy in Cancer Care. London: John Wiley & Sons Ltd; 2011. p. 201-12.

41. Lyons JS. A Communication Theory of Measurement in Human Service Settings. New York: Springer; 2009.

42. Broadstock M, Michie S, Gray J, et al. The psychological consequences of offering mutation searching in the family for those at risk of hereditary breast and ovarian cancer--a pilot study. *Psychooncology*. 2000;**9**:537-48.

Title

Developing A Brief Screening Instrument for Psychosocial Risk Associated with Genetic Testing – A Pan Canadian Cohort Study

Corresponding Author Address

Mary Jane Esplen, PhD
CIHR Scientist and Professor
Department of Psychiatry, Faculty of Medicine, University of Toronto
Behavioral Sciences and Health Research Division
University Health Network
200 Elizabeth Street, 9-EN-242A
Toronto ON M5G 2C4 Canada
Tel: (416) 340-3024
Fax: (416) 340-4739
Email: mesplen@uhnres.utoronto.ca

List of Authors and Institutions

Mary Jane Esplen PhD[1,2,3], Mario Cappelli PhD[4], Jiahui Wong PhD[2,3], Joan Bottorff PhD[5], Jon Hunter MD[2,6], June Carroll MD[6], Michel Dorval PhD[7], Brenda Wilson PhD[8], Judith Allanson MD[9], Kara Semotiuk MSc[10], Melyssa Aronson MSc[10], Louise Bordeleau MD[11], Nicole Charlemagne MSW[1], Wendy Meschino MD[12]

[1]University Health Network, Toronto ON; [2]University of Toronto: Department of Psychiatry, Toronto ON; [3]de Souza Institute, Toronto ON; [4]Children's Hospital of Eastern Ontario, Ottawa ON; [5]University of British Columbia Okanagan, Kelowna BC; [6]Mount Sinai Hospital, Toronto ON; [7]Laval University, Quebec QC; [8]University of Ottawa, Ottawa ON; [9]Eastern Ontario Regional Genetics Centre, Ottawa ON; [10]Zane Cohen Centre for Digestive Diseases, Mount Sinai Hospital, Toronto ON; [11]McMaster University, Hamilton ON; [12]North York General Hospital, Toronto ON.

Keywords:

Genetics, Psychosocial, Screening, Psychosocial Problems, Psychosocial Functioning, Psychological Risk Factors

Word Count: 5115

Abstract:

Objectives: To develop a brief, reliable and valid instrument to screen psychosocial risk among those who are undergoing genetic testing for Adult-Onset Hereditary Disease (AOHD).

Design: A prospective two-phase cohort study.

Setting: 5 genetic testing centres for AOHD such as cancer, Huntingtons, or Hemochromatosis, in ambulatory clinics of tertiary hospitals across Canada.

Participants: 141 individuals undergoing genetic testing were approached and consented to the instrument development phase of the study (Phase I). The Genetic Psychosocial Risk Instrument (GPRI) developed in Phase I was tested in Phase II for item refinement and validation. A separate cohort of 722 individuals consented to the study, 712 completed the baseline package, and 463 completed all follow-up assessments. Most participants were female, at mid-life stage. Individuals in advanced stages of the illness or with cognitive impairment or language barrier were excluded.

Interventions: Phase I: GPRI items were generated from 1) a review of the literature, 2) input from genetic counselors and 3) phase I participants. Phase II: further item refinement and validation was conducted with a second cohort of participants who completed the GPRI at baseline and were followed for psychological distress one month post genetic testing results.

Primary and secondary outcome measures: GPRI, Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), Brief Symptom Inventory (BSI), and Impact of Event Scale (IES).

Results: The final 20 item GPRI had a high reliability - Cronbach's Alpha at 0.81. The construct validity was supported by high correlations between GPRI and BSI and IES. The predictive value was demonstrated by a Receiver Operating Characteristic (ROC) curve of 0.78 plotting GPRI against follow-up assessments using HAM-D and HAM-A.

Conclusions: With a cut off score of 50, GPRI identified 84% of participants who displayed distress post genetic testing results, supporting its potential usefulness in a clinical setting.

Word count: 299
Trial registration: Not applicable

Summary

1) Article Focus

- A significant group of individuals undergoing genetic testing for Adult onset disease experience distress or challenges in adaptation, some might develop depression or anxiety
- Existing psychological screening tools do not take into consideration "risk factors" associated with heritable illness or genetic-related stressors
- A screening tool designed for genetic testing services is a useful tool to guide clinicians in relation to which patients would benefit from added psychosocial support during the genetic testing process.

2) Key Messages

- A subgroup of patients undergoing genetic testing required added psychosocial support to facilitate adaptation to genetic/ risk information. Busy genetic service providers can face challenges to identify these individuals and provide timely interventions or referrals.
- A new brief instrument was designed and validated to identify those individuals at risk for psychological distress such as depression or anxiety who are undergoing genetic testing for adult onset diseases.
- This is the first study to develop and validate a psychological screening instrument for genetic testing field.

3) Strengths and Limitations

- This newly developed tool, Genetic Psychosocial Risk Instrument (GPRI), is the first reported psychosocial screening instrument for use across Adult Onset Hereditary Diseases.
- The GPRI demonstrates promising psychometric properties as a tool designed to assist genetics health care providers determine which of their patients undergoing genetic testing for AOHD is at increased psychological risk and who will benefit from added psychosocial support.
- Study findings are limited by the characteristics of the sample, most participants were female and undergoing testing for BRCA1/2. Future studies could further address the validity of GPRI in male populations and in the rare adult onset hereditary diseases, such as Huntington's disease.

INTRODUCTION

Genetic predisposition is an important determinant of chronic disease and disability. Despite the benefits of genetic testing, such as increased screening or prophylactic interventions, individuals at high risk for serious illness may become increasingly fearful or distressed about the future. In fact, a consistent finding is that the majority of individuals do adjust to genetic test results, however a subset of individuals undergoing genetic testing for Adult Onset Hereditary Disease (AOHD) experience psychological distress, such as anxiety or depressive symptoms. A screening tool, designed for the genetic testing context, would be helpful in assisting geneticists, genetic counselors or primary care providers to identify this particular group for the implementation of at appropriate preventive or follow-up interventions. Herein, we present a newly developed psychological risk screening instrument that can be readily used within a genetic service for AOHD.

Risk Factors and Psychological Impact of Genetic Testing: The Evidence

The knowledge of genetic risk is life-long and individuals and families often find themselves confronted with ongoing need to face issues and make decisions. Examples include decision-making around prevention and treatment options (e.g. increased surveillance, prophylactic surgery, chemoprevention), the need to notify family members, and in relation personal decisions, such as those involving childbearing [1, 2]. Studies utilizing standardized measures of distress (e.g. symptoms of anxiety or depression) have demonstrated that 8 to 25% of individuals undergoing genetic testing experience distress, the level of which falls within the clinical ranges for depression and anxiety [2-5]. Studies that have utilized standardized disease specific measures of distress (i.e. instruments measuring breast/ovarian cancer worry) have demonstrated

higher prevalence levels [6, 7].

The risk factors for psychological symptoms amongst individuals undergoing genetic testing have been delineated in several studies [4, 8, 9]. While there is generally elevated distress using global measures for depression or anxiety among those who receive positive test results [9-11], individuals testing negative or receiving uninformative results may also have adjustment difficulties [12]. For example, individuals may feel guilt or continue to worry about their disease risk [2, 7, 12]. These findings highlight the importance of considering risk factors in addition to the test result itself. Individuals who have elevated psychological symptoms at the pre-test stage and those with a previous psychiatric history (i.e., depression) are particularly at risk for an adverse psychological outcome after testing [2, 8, 9].

Additional risk factors for distress are more specific to the genetics context and include the level of penetrance of the gene mutation or degree of certainty of developing the disease [4]. The perception of control over the disease (including the number of prevention/treatment options) and perception of the immediacy of risk (proximity in age to perceived disease onset) are important predictors [4, 13]. The expectation of a negative test result can play a role in adjustment, as can the context of test results of other family members [9, 14]. As in other medical areas, specific coping styles can affect adjustment [15]. The prior experiences with loss of family members to disease, as well as the developmental level (i.e. young age) of the individual at the time of the loss [2, 3, 16] are significant factors affecting potential adjustment. In addition, the prior experience of giving care to a family member with the disease and lower levels of social support have been associated with poorer adjustment following a positive test result [2-4, 8, 16].

It is clear that there is not one predominant factor, but rather, a series of variables that may contribute to elevated levels of psychological distress [2, 17]. Emotional reactions may impede the assimilation of risk information and the adoption of preventive measures [2, 18]. Psychological distress occurs along a continuum [19, 20] and can be difficult to identify by health professionals [21]. Distress may not become manifest to the health care team until the patient reaches an observable crisis level, i.e. the onset of severe depression or anxiety, or significant conflicts with the family. An early screening instrument would enable healthcare providers to identify patients being at higher psychological risk in order that appropriate support can be given at the right time. In fact, there is now a general consensus that genetic testing should be accompanied by psychological support to promote optimal adjustment [2, 22].

Screening for Psychological Risk Factors- Why is it necessary?

The gold standard for identifying psychologically distressed individuals involves structured clinical interviews administered by a clinical psychologist or psychiatrist [21]. However, it is too costly and often not feasible in genetic clinics. Standardized measures of psychological functioning (e.g. global scales of depression or anxiety) can also be used as a method for identifying distress. However, few clinics use these measures in practice because of personnel and time requirements for scoring and interpretation of them. Furthermore, these instruments tend to identify global symptoms that are consistent with the diagnostic classifications of anxiety and/or depression and may lack sensitivity to the important and unique issues that surround genetic testing; issues that may include concerns about family members, past experiences with an inheritable disease, and uncertainty about risk reduction options [19, 21]. In addition, items on these measures typically focus on symptoms of anxiety or depression, rather on variables

associated with heritable disease or genetic testing or risk, which may pose barriers for use by genetics health service providers who may prefer instruments that, at face value, appear to them and their patients as being clinically more relevant to the genetic testing context.

More recently, new outcome measures designed to assess the psychological impact of receiving genetic information have been developed. For example, the Multidimensional Impact of Cancer Risk Assessment (MICRA) is designed to assess concerns and impacts associated with genetic testing for BRCA1/2 [19] and another tool, the Psychological Adaptation to Genetic Information Scale, is now available [23]. While these measures will require further validation they provide more clinically relevant approaches to capturing specific impacts of genetic information, such as the increased sense of vulnerability often experienced following genetic testing [19, 23].

Measures of global psychological functioning and the evolving outcome measurement tools for the genetics field are not designed to "predict" vulnerability for future distress, but rather, measure current distress levels. Screening, the aim of the tool developed in this study in contrast, is a rapid, cost-effective alternative [21] to prospectively identify individuals who may experience significant difficulty in their attempts to adapt to their genetic information [17]. A screening tool enables providers to offer timely and focused educational and psychosocial interventions to *prevent* future distress.

The primary *objective* of this study was to develop a brief, reliable and valid psychological risk screening instrument for use in the genetic testing context. The new instrument aimed to incorporate empirically based risk factors for psychological symptoms and would need to show a high sensitivity, specificity and predictive validity indicating risk for future distress post genetic testing results. A cutoff point would need to be determined to guide

clinical decisions as to whether or not to refer, further assess, or intervene to reduce an individual's expressed concern.

METHODS AND MATERIALS

The study was carried out from September 2005 to July 2010, with research ethics board approval from participating genetics clinics: Toronto (Mount Sinai Hospital, North York General Hospital, Princess Margaret Hospital); Ottawa (Children's Hospital of Eastern Ontario); and Vancouver (British Columbia Cancer Agency). Individuals beginning the genetic testing process for AOHD at each site were approached by genetic counsellors on the project team for their permission to be contacted about the study. Those who expressed interest were mailed the baseline package that included the informed consent. The informed consent included all components of the study, including questionnaires, follow-up phone calls, telephone interviews, as well as to the release of their genetic testing information to the research team.

A two phase approach was used for this study**: *Phase I:*** *Item Generation and Refinement,* and ***Phase II:*** *Validation*. The multi-stage method [24] takes validation into consideration at each stage of scale development and has been used successfully in previous studies [25].

Phase I: Item Generation and Refinement.

Item generation

To generate items for the Genetic Psychosocial Risk Instrument (GPRI), a literature search was performed for the following AOHDs: Cancer (Hereditary Breast-Ovarian Cancer Syndrome/ Lynch Syndrome), Huntington Disease (HD), and Hemochromatosis. These diseases were selected as they represented the majority of patients attending genetic clinics and had an

associated available psychosocial literature for review. Databases including Cinahl (1982 to 2006), Medline (1966 to 2006), PsychInfo (1985 to 2006), and Pubmed (1985 to 2006) were searched as well as hand search of references from major publications. Keywords included: genetic screening, genetic testing, psychological, psychological well-being, psychological adjustment, stress, adaptation, cancer worry, disease worry, and distress. Selection criteria for the literature review included studies with a follow-up design or review articles. Each selected study was reviewed by two reviewers on its quality of evidence and generalizability using a standardized template. A total of 73 relevant studies were identified among the disease groups: 49 on cancer, 20 on HD, 2 on Hemochromatosis, and 2 described mixed conditions.

Risk factors for psychological distress identified by the literature review provided the basis for item generation. Items were written in a mixed format where respondents were asked for their endorsement of each statement ranging from Yes/No for risk factors of binary nature, to a 5-point likert-type scale for risk factors with stages in frequency and/or intensity. The instrument items were further refined by 10 genetic service providers (3 geneticists, 4 genetic counselors, 2 oncologists, 1 genetics nurse) rating items on *comprehension, readability, and perceived clinical relevance* using a ten-point scale with 0 being "excellent/definitely relevant" and 10 being "very poor/definitely not relevant". Risk factor items were removed if rated above five by more than 3 providers. Providers were also asked to suggest additional risk factor items. These suggestions were checked against the literature for empirical evidence. Following this step, 7 volunteers undergoing genetic testing for AOHDs were recruited to try out the scale for clarity, succinctness and relevance from the clients' perspectives. At this stage, the proposed instrument consisted of 56 items: demographics (4 items); perceived risk (8 items); life events and family history of the disease (8 items); perceived impact of carrying a mutation (9 items);

family communication (6 items); disease specific concerns (5 items); optimism (3 items); social support (3 items), pre-morbid functioning and previous psychiatric history (10 items).

Item refinement:

Subjects: Following informed consent, a convenient sample of 141 participants who had given blood for genetic tests at the Toronto and Ottawa sites completed the GPRI (using a three patients per item ratio) to select the best items for the candidate scale. The participants were middle aged (48.67 ± 13.29), mostly female (77%) testing for hereditary breast cancer, and many (65%) had already suffered the onset of the illness.

Scoring: To ensure that binary items carry an equal weight as the 5-point likert-type items, a score of 5 was assigned to *Yes* and 1 to *No.* A score of 3 or mean-substitute was assigned to *Not Applicable* to allow it to be counted in the total score. Reliability analysis was carried out and a Cronbach's Alpha was set for .75 or higher for the scale to move to the next phase [26]. Any item with an item-total correlation less than .20 was identified for potential removal. Using team consensus, a total of 19 items were removed, combined or substituted, resulting in a 37 item GPRI candidate scale at the end of phase I.

Phase II: Scale Validation

Subjects: Individuals undergoing genetic testing for one of the AOHDs in each of the five study sites were invited to participate: 1) age 18 or above undergoing genetic testing for cancer, HD, or Hemochromatosis; 2) fluent in English; and 3) residing within 1.5 hours driving distance from study site. Although the onset of an AOHD was not an exclusion criterion, individuals in advanced stages of the illness and / or who were unable to consent due to cognitive impairment

were excluded. At baseline, participants were asked to complete a set of self-report questionnaires (e.g. Brief Symptom Inventory, etc.) described below within a one month period following the provision of a blood sample. For those who received a genetic test result, questionnaires were mailed within two weeks to one month of the disclosure of test result. These participants were also telephoned to complete the Hamilton Depression and Hamilton telephone-based Anxiety Scales to further assess depressive and anxiety symptoms. .

Materials**:** At baseline, three psychosocial measures were used: *GPRI Candidate Scale* from Phase I. To facilitate scoring of the scale by genetic providers, scores for response to each item on the GPRI were imbedded in the questionnaire, where clinicians could calculate a total score in less than 5 minutes. *Brief Symptom Inventory* (BSI) The BSI is a 53-item measure of psychological distress that contains three global scales i) depression, ii) anxiety and iii) somatization [27]. It is widely used in medical and psychiatric populations to assess psychological functioning; *Impact of Event Scale (IES)*: The IES is a 15-item, likert-style scale used to assess the experience of a specific stress response and is designed to be easily anchored in relation to a specific stressor or life event. As previously utilized in the genetics literature to assess genetic testing-related distress, the IES items were anchored in relation to the event of "the genetic test result". The IES has two sub-scales: i) intrusive thoughts and feelings associated with the stressful life event, and ii) items associated with patterns of avoidance of certain thoughts, feelings, or situations [28].

Measures at one month post genetic testing results included: the self -reports scales of the BSI, IES and each participant received a telephone call for the telephone-based Hamilton Depression 29-item Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A). The HAM-D evaluates depressed mood, vegetative and cognitive symptoms of depression, and

comorbid anxiety symptoms [29]. The HAM-A quantifies the severity of anxiety symptomatology and consists of 14 items. The HAM-D and HAM-A have demonstrated validity in clinical interview, in person or by telephone [30]. These two instruments were selected as main outcome measures based on the literature that the standardized interview based-rating scales should be used over subjective report scales as the principal outcome criterion in psychological distress both in general practice and in research trials [34]. Cases would be defined by established cut-offs from the literature for HAM-D >=12 [35] or HAM-A >=10 [36]. These cut off points were established for populations in general practice, which was our study population.

The one-month follow-up time point was selected as it is when elevated distress might occur [31]. In addition, the 2-week duration criterion for depression defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) is met by this time frame.

Assessing Psychometric Property of the Scale

As a first step, items were required to have at least an 80% response rate. Second, each item was examined to determine its contribution to the internal consistency of the total 37-item scale. The minimum item-total correlation was set at .20 [32].

A principal components factor analysis with varimax rotation was performed on the candidate scale to examine the factor structure and the loading of the items. To assess the *convergent validity* of the candidate scale, the correlations between baseline GPRI, IES and BSI were calculated. To assess the *sensitivity, specificity and predictive value* of the GPRI, the follow-up HAM-D and HAM-A were used to identify "cases" who met cut offs for either the depression or anxiety symptomatology. For example, participants with a high GPRI at baseline

would be classified as "at risk" for future onset of adjustment difficulties. This would be confirmed by a high HAM-D or HAM-A score or "case" during 1 month follow-up. Similarly, those with a low GPRI score should receive low score in HAM-D or HAM-A as "non-cases". The predictive value of the GRPI, describing the number of test-positives (in our case, high GPRI) who truly have the psychological condition (i.e. cases identified by HAM-D or HAM-A), was tested by a Receiver Operating Characteristic (ROC) curve which visually plotted the true positive rate (sensitivity) over false positive rate (1-specificity). We included cases to be identified by either anxiety and/or depressive symptomatology as both have been reported in the literature [8, 9].

To address the issue of missing follow-up data in a cohort study, as suggested in the literature [33], we tested the assumption that the sub sample with missing data had a similar baseline exposure (similar GPRI) as the non-missing subsample by comparing baseline GPRI between the participants and dropouts. This step assesses if there was systematic bias resulting from the loss of information in the follow-up period.

RESULTS

Participant characteristics

Study packages were mailed to 1129 individuals interested in hearing more about the study. Of these individuals, 722 of them consented and 712 (98%) completed the GPRI. Most participants were tested for the inheritable cancers, while a small percentage of participants were tested for hemochromatosis and HD. Similar to phase I, phase II participants were mostly female, at mid-life stage, and more than half had a past diagnosis of the disease (see table 1).

Insert Table 1 about Here

Of the 712 participants, 85 (12%) did not receive genetic testing results at the scheduled follow-up time and were not eligible for follow-up measures on psychological symptoms in response to a genetic testing result. Of the remaining 627 participants, 152 (24%) did not return the self-administered follow-up questionnaires and 12 (2%) submitted the follow-up questionnaire package but did not complete a standardized telephone interview using HAM-D and HAM-A (up to 4 telephone calls were made to reach each participant). Therefore the final number of participants with complete follow-up data is 463 (74%). The age, and baseline GPRI score between individuals who did not receive genetic testing results (age 51.4±12.7, GPRI 49.3±12.7), those who did not return the follow-up questionnaires (age 48.1±11.6, GPRI 50.2±14.4) and those who completed follow-up measures (age 50.1±12.8, GPRI 49.1±13.5) were compared. There was no statistically significant group difference (ANOVA and all post-hoc comparisons $p>0.05$).

Because of the similarity between the dropouts and completers, we proceeded with reliability and validity analysis of the tool using the subsample that provided outcome data.

We carried out the calculations for distress level, for example, for depression and anxiety symptoms using the BSI data, for specific distress associated a genetic test result using the IES. Approximately, 13.0% to 20.1% of participants reached the threshold of moderate to severe distress respectively (see table 2).

Insert Table 2 about Here

HAM-D and HAM-A interview data from 463 participants were used as a further validation tool to measure psychological symptoms post genetic testing results. Defined by cut-offs for HAM-D >=12 [35] or HAM-A >=10 in the literature [36], the rates for psychological

distress of either depression or anxiety was 13.7% (N=63). The rate was 13% for HD, 15% for breast cancer and 7% for Lynch Syndrome.

Reliability and Factor Analysis

A reliability analysis was performed on 37 items. Twenty items belonging to 18 questions were selected based on the criteria for item selection described in the methods section. The Cronbach's alpha of the 20 item GPRI was 0.81 suggesting a good level of internal consistency.

The factor analysis resulted in a psychometrically sound 3-factor solution, with subscales representing the dimensions of: 1) *Perceived impact and personal adjustment to genetic testing* (12 items); 2) *Past history of mental health concerns* (5 items) and 3) *Personal history/family history/loss to cancer* (3 items). All three factors met the minimum Eigenvalue criteria of 1.

The first, 12-item factor (ALPHA = 0.85), accounting for 22% of the variance, includes items associated with the anticipated or experienced impact of being at high risk for AOHD. Example items included: "My worries about the disease affect my daily mood"; "The disease for which I am at risk is currently causing a significant disruption in my family life".

The second 5-item factor (ALPHA = 0.76), accounted for an additional 14% of the total variance, and reflected a sense of a person's past history or vulnerability in the area of mental health , e.g. "I have had emotional problems in the past", These items have been used in other medical health areas [37, 38] and tend to be predictive of maladjustment [20] following a life event.

The third 3 item factor (ALPHA = 0.08), accounted for 8% of the total variance and pertained to personal or family-related experiences associated with the hereditable disorder for which the participant is undergoing testing. . Examples include: "I have a personal diagnosis of

the disease for which I am receiving counseling"; "I lost a close family member to the disease for which I am receiving counseling"; and "I have taken care of a very ill parent or another close family member". These 3 final items had low item total correlation because they were different from the rest of the items in that they focused on direct experiences related to the illness, rather than psychosocial-related items. These items were kept in the scale as they contributed significantly to the overall variance, and correlated highly with HAM-D and HAM-A. To determine the relationships between the three factors/subscales, correlations were computed. Factor1 and factor2 had moderate correlations with each other (factor1/factor2 $r=0.30$, $p<0.01$). The correlation of the first two factors with factor3 was much lower as expected (factor1/factor3 $r=0.06$, and factor2/factor3 $r=0.01$, not statistically significant). These results support the multidimensional character of the GPRI scale (see Table 3).

Insert Table 3 about Here

One additional statement "I am interested in talking to a counselor about one or more of these concerns" was added to the tool at the end as suggested by participants and providers to remind them the option of seeing a counselor if required. This statement is not part of the items examined during the instrument development and therefore does not carry a score.

The total score for the 20 item GPRI ranged from 20 to 100, with a sample mean 49.36 ± 13.23. The total was calculated by the sum of the raw scores for each of the statements. Females had a significantly higher score for the GPRI than males (50.37 ± 13.14 vs. 41.91 ± 11.47, $p<0.01$), and participants testing for HD had a higher, but non-significant score than participants testing for cancer (52.24 ± 13.24 vs. 49.37 ± 13.22, n.s.).

Validity

Construct validity – correlations: The GPRI was assessed for its correlation with other standardized self-report measures of psychological functioning collected at baseline. Convergent validity was demonstrated by the correlation between the GPRI and the following measures: a positive correlation with the IES total score at r = .51, p< .001, and with BSI at r = .58, p< .001.

Sensitivity, specificity and the predictive value of GPRI for future distress: The telephone interview-based HAM-D and HAM-A were used to identify subjects who presented specific psychological symptoms of distress such as depression and/or anxiety during the one month post genetic testing follow-up. A total of 63 "cases" (13.6% of 463 completers) were identified as having psychological distress levels above specified thresholds defined in the methods section for either anxiety or depression symptoms or both. About 23% among participants testing positive met the distress threshold, as did 10% among those with negative results, and 20% among uninformative. Participants scoring above HAM-D (N=55) threshold had significantly higher GPRI scores than participants below the threshold (N=408) (61.12±13.27 vs. 47.91±12.27, p<0.01). Same patterns were observed for HAM-A high (N=40) vs. low (N=423) (62.53±12.92 vs. 48.25± 12.43, p<0.01).

Other demographic characteristics of these 63 subjects include: most were female and undergoing testing for BRCA1/2, which was similar to the whole sample of 712 (table 1). Compared with the whole sample, these subjects had a slightly higher percentage of personal history of cancer (65% vs. 62%), higher rate of recent significant event of loss (56% vs. 47%), greater percentage reporting disease worries affecting mood (54.8% vs. 27%), having a feeling of sadness in the past month (46% vs. 17%) and anxiousness in the past month (33% vs. 17%). Our instrument captured all of these characteristics of this subsample.

The predictive value of a test describes how many of the test-positives (in this case, a high score on GPRI) truly have the psychological condition. An ROC curve was used to plot the true positive rate (sensitivity) over the false positive rate (1-specificity). A good ROC curve rises sharply, indicating a high proportion in true positive and a low proportion of false positives. The ROC curve for the GPRI was 0.78, which is considered as an indicator of an adequate screening instrument [39].

An important purpose of the GRPI in our study was to identify individuals at risk for post genetic testing psychological distress. Therefore, the cutoff value was set to maximize sensitivity – in another word, not to miss detecting a "case". Using a GPRI cut off score of 50, the instrument was able to predict 84% of the "cases" identified by HAM-D or HAM-A conducted post genetic testing results, with a specificity value of 60% (Figure 1).

Insert Figure 1 about Here

DISCUSSION

The aim of this study was to develop a brief, easy-to-use psychosocial screening instrument specific for the genetic testing context and to examine its reliability and validity (Appendix A). To our knowledge this is the first report of a psychosocial screening instrument for use across AOHD. Unlike current psychological instruments used mainly in research studies in genetics clinics to identify existing global symptoms of depression and anxiety, or impacts, the GPRI assesses *psychological risk factors*, such as the specific anticipated impacts of a genetic testing result and the perception of the disease. The GPRI demonstrates promising psychometric properties as a tool designed to assist genetics health care providers determine which of their

patients undergoing genetic testing for AOHD is at increased psychological risk and should likely be considered for additional psychosocial support to facilitate adjustment to a test result.

A high reliability was demonstrated by a Cronbach's Alpha at 0.81, moderate to high item-total correlation and inter-item correlation of the whole scale. The construct validity of the scale was supported by high correlations between the GPRI and standardized psychological measures (BSI, IES). The clinical utility and predictive value of the GPRI was supported as well. A GPRI score above the cutoff of 50 at baseline was able to predict 84% of "distress" cases identified by HAM-D or HAM-A, a strong indicator of its potential usefulness in a clinical setting.

A brief self-administered screening tool will be easy and likely highly acceptable for incorporation into genetics clinics. The GPRI can be completed and scored quickly during clinical visits and without additional burden to patients and health providers. In addition, by focusing specifically on known risk factors associated with inheritable illness, the instrument will be perceived as being more clinically relevant and acceptable to patients. Patients with higher GPRI scores can be flagged and either receive telephone follow-up to further assess concerns or potential distress or be invited back for an appointment for further assessment and required psychological treatment.

Alternatively, genetic clinics with available psychosocial personnel could utilize the tool to guide referrals for a formal psychosocial assessment that can further explore and address specific self-reported psychological factors. For example, in the case where an individual is particularly fearful of developing an illness or is concerned about specific impacts, such as expecting relationship or family communications difficulties, information on communication strategies, personal coaching or family–based interventions could be employed to support the

individual. For an individuals who reports a past history of psychological illness, a mental health professional could further assess current psychological functioning and implement specific approaches, and could offer cognitive-behavioral strategies or psychotropic medication to assist in the management of anxiety or depressive symptoms [40]. Several items incorporate variables related to heritable disease experiences and associated perceptions which can be used to guide educational interventions to correct any myths or beliefs.

The scale appeared highly acceptable to patients. A high face validity will contribute to better scale uptake being perceived as "user friendly" and clinically relevant, compared for example, to a standardized psychological instrument on depression, which have demonstrated some barriers to clinic uptake [19]. The GPRI in contrast might be considered as a "communimetric measure", that is, the items themselves are useful for the clinician in communicating concerns about specific areas of functioning directly with the patient [41].

Left untreated, significant levels of psychological symptoms may lead to lower quality of life [40], and lower satisfaction with genetics services [21]. A psychological screening approach allows both for careful monitoring during a known stressful period-that of awaiting test results [42], and provides an opportunity for any planned follow-up care. Flagging those individuals who might benefit most from psychosocial care also best utilizes the often limited psychological resources in genetic clinics [2, 20, 21].

Our study findings are limited by the characteristics of the sample, in that most participants were female and undergoing testing for *BRCA1/2*. This pattern is similar to that observed in the literature on genetic testing for AOHD, which is predominantly focused on Hereditary Breast-Ovarian Cancer Syndrome. We attempted to obtain a larger sample of individuals undergoing genetic testing for HD or Lynch Syndrome which would presumably

provide a greater sample of males. However, these sample pools were much smaller. However, this study and the resulting GPRI represent an attempt to begin the development of a general tool that addresses concerns that are relevant across genetic samples. Our belief stemming from clinical practice and the associated literature suggest that the identified mental health issues or adjustment risk factors are not disease specific. We suggest that future studies further address the validity of GPRI in male populations and in the rare adult onset hereditary diseases, such as HD. Future studies should also include randomized controlled trials to assess the effectiveness of the GPRI in predicting distress, its impact on referral patterns, patient and provider satisfaction, as well as on cost-effectiveness. The GPRI could also be evaluated in primary care settings where genetics services might be offered more frequently to meet the demand.

CONCLUSIONS

This is the first study to develop a screening tool specifically to help identify individuals undergoing genetic testing for AOHD who are at increased psychological risk. The study resulted in an easy to use, 20-item scale consisting of 3 factors with promising psychometric properties. The GPRI has the potential to be used as a clinical screening tool and as a validated measure for future studies. Future work can examine its impact on clinical referral patterns within the field of genetics, and on its acceptability, reliability and validity with larger samples of individuals undergoing genetic testing for HD, Lynch Syndrome, and potentially for emerging new genetic tests, such as for cardiac or psychiatric disorders.

Acknowledgement

The first author is a recipient of a career scientist award from the Canadian Institutes of Health Research (CIHR) and the Ontario Women's Health Council. This study was funded by Canadian Institutes of Health Research (CIHR) Grant No. AHC 73144. We would like to express our gratitude to all the genetic testing patients who participated in our study. Thank you for your contribution towards this very important work and the development of the instrument. Thank you also to the genetic counselors and clinic staff from the participating genetic centers who assisted in recruitment: Children's Hospital of Eastern Ontario (Eastern Ontario Regional Genetics Centre); North York General Hospital (Clinical Genetics); Mount Sinai Hospital (Familial GI Cancer Registry & Familial Breast Cancer Clinic); Princess Margaret Hospital (Familial Breast & Ovarian Cancer Clinic); and BC Cancer Agency (Hereditary Cancer Program). We would also like to thank the research staff for their commitment and hard work to complete this national multi-site study. Finally, the team would like to pay special recognition to the late Dr. Anne Summers, who was co-investigator on the team. Her dedication to the need for empirically based tools and her strong vision to support recipients of new genetic technology were key influences in the conceptualization, funding and completion of this study.

Ethics: Research Ethics Board approval was obtained at all five participating sites: Toronto (Mount Sinai Hospital, North York General Hospital, Princess Margaret Hospital); Ottawa (Children's Hospital of Eastern Ontario); and Vancouver (British Columbia Cancer Agency).

Data Sharing Statement: There is no additional data available

Conflict of Interest: The authors do not have any conflict of interest to disclose.

Funding: This study was funded by Canadian Institutes of Health Research (CIHR) Grant No. AHC 73144.

Contributorship Statements

Dr. Mary Jane Esplen

Principal Applicant responsible for leading all aspects of the research, oversees budget, hiring staff, supervising data collection, analysis and interpretation, and writing of all manuscripts and reports.

Dr. Mario Cappelli

Co-principal inv. responsible for assisting in item generation and refinement, the implementation of data collection, interpretation of findings and writing of manuscripts and reports.

Dr. Jiahui Wong

Co- Applicant responsible assisting in instrument development, statistical procedures, sampling and interpretation of findings and writing of manuscripts and reports.

Dr. Joan Bottorff

Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services, development of guidelines and writing of manuscripts and reports.

Dr. Jon Hunter

Co-Applicant responsible for assisting in item generation and refinement, guideline development, interpretation of findings and writing of manuscripts and reports.

Dr. June Carroll

Co-Applicant responsible for assisting in item generation and refinement, implementation of the screening validation strategy and development of guidelines, interpretation of findings and writing of manuscripts and reports.

Dr. Michel Dorval

Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services, interpretation of findings and writing of manuscripts and reports.

Dr. Brenda Wilson

Co-Applicant responsible for co-leading the implementation of the consensus guidelines components of the proposed study. Will assist in item generation for tool, interpretation of findings, writing of manuscripts and reports.

Dr. Judith Allanson

Co-Applicant responsible for refining of items, guiding the recruitment of providers/patients and testing of the instrument in genetic services, development of guidelines and writing of manuscripts and reports.

Ms. Kara Semotiuk

Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services and development of guidelines, and writing of manuscripts and reports.

Ms. Melyssa Aronson

Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services, development of guidelines and writing of manuscripts and reports.

Dr. Louise Bordeleau

Co-Applicant responsible for overseeing recruitment at MSH and UHN site in Toronto, testing of instrument and interpretation of findings, writing of manuscripts and reports.

Ms. Nicole Charlemagne

Project coordinator, responsible for: patient recruitment and follow-up; assisting in item generation, refinement, and overall layout and design of tool; data collection, data entry, and data clean-up; revisions and submission of manuscript.

Dr. Wendy Meschino

Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services, interpretation of findings and writing of manuscripts and reports.

REFERENCES

1. Lerman C, Croyle RT. Emotional and behavioral responses to genetic testing for susceptibility to cancer. *Oncology (Williston Park)*. 1996;**10**:191-5, 9; discussion 200-2.

2. Bleiker EM, Hahn DE, Aaronson NK. Psychosocial issues in cancer genetics--current status and future directions. *Acta Oncol*. 2003;**42**:276-86.

3. Wellisch DK, Lindberg NM. A psychological profile of depressed and nondepressed women at high risk for breast cancer. *Psychosomatics*. 2001;**42**:330-6.

4. Broadstock M, Michie S, Marteau T. Psychological consequences of predictive genetic testing: a systematic review. *Eur J Hum Genet*. 2000;**8**:731-8.

5. Ho SM, Ho JW, Bonanno GA, et al. Hopefulness predicts resilience after hereditary colorectal cancer genetic testing: a prospective outcome trajectories study. *BMC Cancer*. 2010;**10**:279.

6. Trask PC, Paterson AG, Wang C, et al. Cancer-specific worry interference in women attending a breast and ovarian cancer risk evaluation program: impact on emotional distress and health functioning. *Psychooncology*. 2001;**10**:349-60.

7. Coyne JC, Kruus L, Racioppo M, et al. What do ratings of cancer-specific distress mean among women at high risk of breast and ovarian cancer? *Am J Med Genet A*. 2003;**116A**:222-8.

8. Marteau TM, Croyle RT. The new genetics. Psychological responses to genetic testing. *BMJ*. 1998;**316**:693-6.

9. Meiser B. Psychological impact of genetic testing for cancer susceptibility: an update of the literature. *Psychooncology*. 2005;**14**:1060-74.

10. Hamilton JG, Lobel M, Moyer A. Emotional distress following genetic testing for hereditary breast and ovarian cancer: a meta-analytic review. *Health Psychol*. 2009;**28**:510-8.

11. Shaw C, Abrams K, Marteau TM. Psychological impact of predicting individuals' risks of illness: a systematic review. *Soc Sci Med*. 1999;**49**:1571-98.

12. Dorval M, Gauthier G, Maunsell E, et al. No evidence of false reassurance among women with an inconclusive BRCA1/2 genetic test result. *Cancer Epidemiol Biomarkers Prev*. 2005;**14**:2862-7.

13. Cameron LD, Sherman KA, Marteau TM, et al. Impact of genetic risk information and type of disease on perceived risk, anticipated affect, and expected consequences of genetic tests. *Health Psychol*. 2009;**28**:307-16.

14. Smith KR, West JA, Croyle RT, et al. Familial context of genetic testing for cancer susceptibility: moderating effect of siblings' test results on psychological distress one to two weeks after BRCA1 mutation testing. *Cancer Epidemiol Biomarkers Prev*. 1999;**8**:385-92.

15. Dougall AL, Smith AW, Somers TJ, et al. Coping with genetic testing for breast cancer susceptibility. *Psychosom Med*. 2009;**71**:98-105.

16. Esplen MJ, Urquhart C, Butler K, et al. The experience of loss and anticipation of distress in colorectal cancer patients undergoing genetic testing. *J Psychosom Res*. 2003;**55**:427-35.

17. Zabora JR. Screening procedures for psychological distress. In: Holland JC, editor. Psycho-Oncology. New York: Oxford University Press; 1998. p. 653-62.

18. Watson M, Lloyd S, Davidson J, et al. The impact of genetic counselling on risk perception and mental health in women with a family history of breast cancer. *Br J Cancer*. 1999;**79**:868-74.

19. Cella D, Hughes C, Peterman A, et al. A brief assessment of concerns associated with genetic testing for cancer: the Multidimensional Impact of Cancer Risk Assessment (MICRA) questionnaire. *Health Psychol*. 2002;**21**:564-72.

20. Zabora J, BrintzenhofeSzoc K, Curbow B, et al. The prevalence of psychological distress by cancer site. *Psychooncology*. 2001;**10**:19-28.

21. Thewes B, Meiser B, Tucker K, et al. Screening for psychological distress and vulnerability factors in women at increased risk for breast cancer: A review of the literature. *Psychology, Health & Medicine*. 2003;**8**:289-303.

22. Howell D, Keller-Olaman S, Oliver T, et al. A Pan-Canadian Practice Guideline: Screening, Assessment and Care of Psychosocial Distress (Depression, Anxiety) in Adults with

Cancer. Toronto: Canadian Partnership Against Cancer (Cancer Journey Action Group) and the Canadian Association of Psychosocial Oncology2010.

23. Read CY, Perry DJ, Duffy ME. Design and psychometric evaluation of the Psychological Adaptation to Genetic Information Scale. *J Nurs Scholarsh*. 2005;**37**:203-8.

24. Jackson D. A sequential system for personality scale development. In: Spielberger C, editor. Current Topics in Clinical and Community Psychology. New York: Academic Press; 1970. p. 61-96.

25. Stuckless N, Goranson R. The vengeance scale: Development of a measure of attitudes toward revenge. *Journal of Social Behavior and Personality*. 1992;**7**:25-42.

26. Briggs SR, Cheek JM. The role of factor analysis in the development and evaluation of personality scales. *Journal of Personality*. 1986;**54**:106-48.

27. Derogatis LR. The brief symptom inventory (BSI). Administration, Scoring and Procedures Manual. 3rd ed. New York: National Computer Systems; 1993.

28. Horowitz MJ, Wilner N, Alvarez W. Impact of Events Scale: A Measure of Subjective Stress. *Psychosomatic Medicine*. 1979;**41**:209-18.

29. Hamilton MA. A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*. 1960;**23**:56-23.

30. Katzelnick DJ, Simon GE, Pearson SD, et al. Randomized trial of a depression management program in high utilizers of medical care. *Arch Fam Med*. 2000;**9**:345-51.

31. DudokdeWit AC, Tibben A, Duivenvoorden HJ, et al. Predicting adaptation to presymptomatic DNA testing for late onset disorders: who will experience distress? Rotterdam Leiden Genetics Workgroup. *J Med Genet*. 1998;**35**:745-54.

32. Walsh W, Betz N. Tests and Assessments. New Jersey: Prentice Hall Inc; 1985.

33. Melnick EL, Everitt BS. Quantitative risk analysis and assessment. Hebokea NJ: John Wiley & Sons; 2008.

34. Moller HJ. Rating depressed patients: observer- vs self-assessment. *Eur Psychiatry*. 2000;**15**:160-72.

35. Aben I, Verhey F, Lousberg R, et al. Validity of the beck depression inventory, hospital anxiety and depression scale, SCL-90, and hamilton depression rating scale as screening instruments for depression in stroke patients. *Psychosomatics*. 2002;**43**:386-93.

36. Pasquini M, Biondi M, Costantini A, et al. Detection and treatment of depressive and anxiety disorders among cancer patients: feasibility and preliminary findings from a liaison service in an oncology division. *Depress Anxiety*. 2006;**23**:441-8.

37. Beck CT. A checklist to identify women at risk for developing postpartum depression. *J Obstet Gynecol Neonatal Nurs*. 1998;**27**:39-46.

38. Reid AJ, Biringer A, Carroll JD, et al. Using the ALPHA form in practice to assess antenatal psychosocial health. Antenatal Psychosocial Health Assessment. *CMAJ*. 1998;**159**:677-84.

39. Goutham R. What is an ROC curve? *The Journal of Family Practice*. 2003;**52**:695.

40. Esplen MJ, Hunter J. Therapy in the Setting of Genetic Predisposition to Cancer' in 'Handbook of Psychotherapy in Cancer Care. In: Watson M, Kissane D, editors. Handbook of Psychotherapy in Cancer Care. London: John Wiley & Sons Ltd; 2011. p. 201-12.

41. Lyons JS. A Communication Theory of Measurement in Human Service Settings. New York: Springer; 2009.

42. Broadstock M, Michie S, Gray J, et al. The psychological consequences of offering mutation searching in the family for those at risk of hereditary breast and ovarian cancer--a pilot study. *Psychooncology*. 2000;**9**:537-48.

Table 1
Description of Phase II Participants Characteristics (N=712)

Variables in GPRI*		
Age in years: mean (SD)		49.80 (+12.53), range 18-80, median 50.00
Gender: n (%)	Male Female	85 (12%) 627 (88%)
Type of AOHD being tested: n (%)	Cancer (BRCA) Cancer (other, ie, Colon) Huntington disease Hemochromatosis	580 (82%) 90 (13%) 31 (4%) 5 (1%)
Personal history of disease being tested: n (%)		441 (62%)
Recent significant event (diagnosis of or loss of significant others to the disease being tested): n (%)		333 (47%)
Disease worries affect daily mood (strongly agree or somewhat agree): n (%)		189 (27%)
Sad in the past month (often or almost all the time): n (%)		121 (17%)
Anxious in the past month (often or almost all the time) n (%)		121 (17%)

* Note: there are missing data for some GRPI variables. The total count for each variable do not necessarily add up to 712

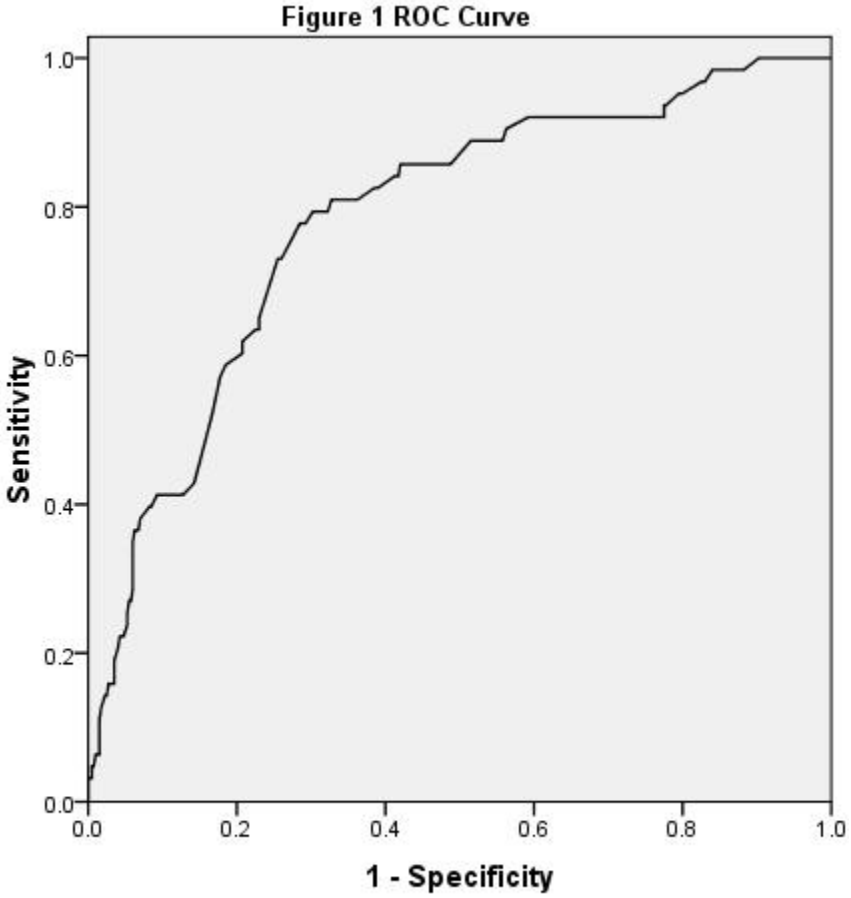
Table 2
Psychological Symptom of Distress 1 Month Post Genetic Testing Results By Disease Type (N=475)

	Overall N (%)	Huntington	*BRCA*	Other Cancer
IES intrusion >=17[a]	60 (13.0%)	5 (23.8%)	51 (12.5%)	4 (9.5%)
IES avoidance >=17[a]	65 (13.7%)	5 (23.8%)	57 (14.0%)	3 (7.1%)
BSI-18 total >=13[b]	95 (20.1%)	6 (28.6%)	86 (21.1%)	3 (7.1%)

a. Shemesh E. et al (2004) Posttraumatic stress, non adherence, and adverse outcome in survivors of a myocardial infarction. Psychosomatic Medicine, 66: 521-526
b. Zabora et al (2001): A new psychosocial screening instrument for use with cancer patients. Psychosomatics, 42:241–246

Table 3
GPRI Factor Solutions and Factor Loadings

	Factor Loadings	Commu-nalities	Item-Total	Item Mean
• My worries about the disease affect my daily mood	.759	.652	.582	2.22
• I worry often about my risk of getting the disease	.742	.551	.529	2.67
• I am concerned about my risk of getting the disease	.656	.484	.472	3.28
• I have generally felt nervous and anxious in the past month	.652	.538	.600	2.54
• I have generally felt sad in the past month	.627	.524	.572	2.58
• If I learn that I have a genetic mutation, … I will have more problems in my life	.617	.406	.399	2.79
…I will have difficulties with my family relationships	.513	.324	.424	1.62
… I will change plans for my career	.451	.228	.262	2.08
• The disease is currently causing a significant disruption in my family life	.568	.408	.463	2.42
• I am worried that my test result will impact on my relationship with my significant other	.546	.308	.383	2.54
• I am worried about talking to my children about the heritable nature of the disease for which I am being tested	.522	.326	.453	2.04
• I feel guilty that I might pass on the disease risk to my children	.508	.276	.414	3.11
Factor 1: Anticipated or experienced impact of having a disease risk or genetic mutation: 12 statements, Cronbach's alpha = .85, inter – item correlation = .32, variance explained = 22%				
• I have had emotional problems in the past	.796	.655	.423	2.66
• I have been diagnosed with a depressive or anxiety disorder in the past	.769	.596	.349	2.01
• I have had counselling with a mental health professional in the past	.762	.593	.433	2.85
• I have had emotional problems that led me to thoughts about suicide	.623	.389	.262	1.45
• I am now seeing a counselor for one or more of these emotional concerns	.509	.272	.274	1.35
Factor 2: Personal history or vulnerability to mental health issues or symptoms: 5 items, Cronbach's alpha = .76, inter – item correlation = .39, variance explained = 14%				
• I have taken care of a very ill parent or another close family member	.687	.493	.116	2.36
• I lost a close family member (e.g. parent/ sibling) to the disease for which I am receiving counseling/testing	.667	.445	-.002	2.87
• I have/had a personal diagnosis of the disease for which I am receiving counseling/testing	-.642	.413	-.073	3.47
Factor 3: Personal or family history of the genetic disease being tested in the clinic: 3 items, Cronbach's alpha = .08, inter – item correlation = .03, variance explained = 8%				



Appendix A Genetic Psychosocial Risk Instrument (GPRI)

The purpose of this questionnaire is to help identify individuals who may need additional support while going through genetic testing. The questions are about your life experiences and feelings about the disease for which you are receiving genetic testing/counseling. Please note that whenever the word "disease" is used, it is referring to the disease for which you are having genetic testing and/or counseling. Please read each statement carefully, then respond by placing a firm checkmark in the most appropriate space.

Name:	Date (dd / mm / yyyy):

1. I have/had a personal diagnosis of the disease for which I am receiving counseling/testing (5) Yes (1) No
2. I have taken care of a very ill parent or another close family member (e.g. sibling) (0) Yes (1) No
   If yes, the illness was related to the condition for which I am receiving counseling/testing (5) Yes (3) No
3. I lost a close family member (e.g. parent/sibling) to the disease for which I am receiving counseling/testing (5) Yes (1) No
   If yes, please indicate who the family member was who died (check all that apply):
   (0) a parent (0) a sibling (0) other (specify)_____

	Strongly agree	Somewhat agree	Neither agree/disagree	Somewhat disagree	Strongly disagree	Not applicable
4. If I learn that I have a genetic mutation, I believe that:						
a. I will have more problems in my life	5	4	3	2	1	0
b. I will change plans for my career/ profession	5	4	3	2	1	3
c. I will have difficulties in my family relationships	5	4	3	2	1	3
5. The disease for which I am at risk is currently causing a significant disruption in my family life	5	4	3	2	1	3
6. I am worried that my test result will impact on my relationship with my significant other (or future partner)	5	4	3	2	1	3
7. I am worried about talking to my children (young or adult) about the heritable nature of the disease for which I'm being tested	5	4	3	2	1	3
8. My worries about the disease affect my daily mood	5	4	3	2	1	3
9. I worry often about my risk of getting the disease	5	4	3	2	1	3
10. I am concerned about my risk of getting the disease	5	4	3	2	1	3
11. I feel guilty that I might pass on the disease risk to my children	5	4	3	2	1	3

	Almost all of the time	Often	Sometimes	Hardly ever	Not at all
12. I have generally felt sad in the past month	5	4	3	2	1
13. I have generally felt nervous and anxious in the past month	5	4	3	2	1

14. I have had emotional problems in the past (5) Yes (1) No
15. I have had counseling with a counselor and/or a mental health professional in the past (5) Yes (1) No
16. I have been diagnosed with a depressive or anxiety disorder in the past (5) Yes (1) No
17. I have had emotional problems that led me to have thoughts about suicide (5) Yes (1) No
18. I am now seeing a counselor for one or more of these emotional concerns (5) Yes (1) No

19. I am interested in talking with a counsellor about one or more of these concerns (0) Yes (0) No

Instruction to the user: Item #19 is for referral purpose only, no score is assigned. The remaining items all have assigned scores. Because item #4 has three sub-statements, a total of 20 statements/items are included in the scoring.
Please sum the score of all items & enter the total score here _____. If it is 50 or greater, and if #19 is Yes, then a psychosocial referral is recommended.

Developing A Brief Screening Instrument for Psychosocial Risk Associated with Genetic Testing – A Pan Canadian Cohort Study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-002227.R2
Article Type:	Research
Date Submitted by the Author:	09-Feb-2013
Complete List of Authors:	Esplen, Mary Jane; Toronto General Hospital, Behavioural Science & Health Research Division; de Souza Institute, Cappelli, Mario; Children's Hospital of Eastern Ontario, ; University of Ottawa, Wong, Jiahui; de Souza Institute, ; University of Toronto, Department of Psychiatry Bottorff, Joan; University of British Columbia Okanagan, Hunter, Jon; Mount Sinai Hospital, ; University of Toronto, Department of Psychiatry Carroll, June; Mount Sinai Hospital, Dorval, Michel; Laval University, Wilson, Brenda; University of Ottawa, Allanson, Judith; Childrens Hospital of Eastern Ontario, Genetics Semotiuk, Kara; Mount Sinai Hospital, Zane Cohen Centre for Digestive Diseases Aronson, Melyssa; Mount Sinai Hospital, Zane Cohen Centre for Digestive Diseases Bordeleau, Louise; McMaster University, Charlemagne, Nicole; Toronto General Hospital, Behavioural Science & Health Research Division Meschino, Wendy; North York General Hospital,
Primary Subject Heading:	Genetics and genomics
Secondary Subject Heading:	Mental health
Keywords:	Genetics < TROPICAL MEDICINE, Cancer, Psychosocial, Screening, Psychosocial adjustment, behavioural science

Title

Developing A Brief Screening Instrument for Psychosocial Risk Associated with Genetic Testing – A Pan Canadian Cohort Study

Corresponding Author Address

Mary Jane Esplen, PhD
CIHR Scientist and Professor
Department of Psychiatry, Faculty of Medicine, University of Toronto
Behavioral Sciences and Health Research Division
University Health Network
200 Elizabeth Street, 9-EN-242A
Toronto ON M5G 2C4 Canada
Tel: (416) 340-3024
Fax: (416) 340-4739
Email: mesplen@uhnres.utoronto.ca

List of Authors and Institutions

Mary Jane Esplen PhD[1,2,3], Mario Cappelli PhD[4], Jiahui Wong PhD[2,3], Joan Bottorff PhD[5], Jon Hunter MD[2,6], June Carroll MD[6], Michel Dorval PhD[7], Brenda Wilson PhD[8], Judith Allanson MD[9], Kara Semotiuk MSc[10], Melyssa Aronson MSc[10], Louise Bordeleau MD[11], Nicole Charlemagne MSW[1], Wendy Meschino MD[12]

[1]University Health Network, Toronto ON; [2]University of Toronto: Department of Psychiatry, Toronto ON; [3]de Souza Institute, Toronto ON; [4]Children's Hospital of Eastern Ontario, Ottawa ON; [5]University of British Columbia Okanagan, Kelowna BC; [6]Mount Sinai Hospital, Toronto ON; [7]Laval University, Quebec QC; [8]University of Ottawa, Ottawa ON; [9]Eastern Ontario Regional Genetics Centre, Ottawa ON; [10]Zane Cohen Centre for Digestive Diseases, Mount Sinai Hospital, Toronto ON; [11]McMaster University, Hamilton ON; [12]North York General Hospital, Toronto ON.

Keywords:

Genetics, Psychosocial, Screening, Psychosocial Problems, Psychosocial Functioning, Psychological Risk Factors

Word Count: 5124

Abstract:

Objectives: To develop a brief, reliable and valid instrument to screen psychosocial risk among those who are undergoing genetic testing for Adult-Onset Hereditary Disease (AOHD).

Design: A prospective two-phase cohort study.

Setting: 5 genetic testing centres for AOHD such as cancer, Huntingtons, or Hemochromatosis, in ambulatory clinics of tertiary hospitals across Canada.

Participants: 141 individuals undergoing genetic testing were approached and consented to the instrument development phase of the study (Phase I). The Genetic Psychosocial Risk Instrument (GPRI) developed in Phase I was tested in Phase II for item refinement and validation. A separate cohort of 722 individuals consented to the study, 712 completed the baseline package, and 463 completed all follow-up assessments. Most participants were female, at mid-life stage. Individuals in advanced stages of the illness or with cognitive impairment or language barrier were excluded.

Interventions: Phase I: GPRI items were generated from 1) a review of the literature, 2) input from genetic counselors and 3) phase I participants. Phase II: further item refinement and validation was conducted with a second cohort of participants who completed the GPRI at baseline and were followed for psychological distress one month post genetic testing results.

Primary and secondary outcome measures: GPRI, Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), Brief Symptom Inventory (BSI), and Impact of Event Scale (IES).

Results: The final 20 item GPRI had a high reliability - Cronbach's Alpha at 0.81. The construct validity was supported by high correlations between GPRI and BSI and IES. The predictive value was demonstrated by a Receiver Operating Characteristic (ROC) curve of 0.78 plotting GPRI against follow-up assessments using HAM-D and HAM-A.

Conclusions: With a cut off score of 50, GPRI identified 84% of participants who displayed distress post genetic testing results, supporting its potential usefulness in a clinical setting.

Word count: 299
Trial registration: Not applicable

Summary

1) Article Focus

- A significant group of individuals undergoing genetic testing for Adult onset disease experience distress or challenges in adaptation, some might develop depression or anxiety
- Existing psychological screening tools do not take into consideration "risk factors" associated with heritable illness or genetic-related stressors
- A screening tool designed for genetic testing services is a useful tool to guide clinicians in relation to which patients would benefit from added psychosocial support during the genetic testing process.

2) Key Messages

- A subgroup of patients undergoing genetic testing required added psychosocial support to facilitate adaptation to genetic/ risk information. Busy genetic service providers can face challenges to identify these individuals and provide timely interventions or referrals.
- A new brief instrument was designed and validated to identify those individuals at risk for psychological distress such as depression or anxiety who are undergoing genetic testing for adult onset diseases.
- This is the first study to develop and validate a psychological screening instrument for genetic testing field.

3) Strengths and Limitations

- This newly developed tool, Genetic Psychosocial Risk Instrument (GPRI), is the first reported psychosocial screening instrument for use across Adult Onset Hereditary Diseases.
- The GPRI demonstrates promising psychometric properties as a tool designed to assist genetics health care providers determine which of their patients undergoing genetic testing for AOHD is at increased psychological risk and who will benefit from added psychosocial support.
- Study findings are limited by the characteristics of the sample, most participants were female and undergoing testing for BRCA1/2. Future studies could further address the validity of GPRI in male populations and in the rare adult onset hereditary diseases, such as Huntington's disease.

INTRODUCTION

Genetic predisposition is an important determinant of chronic disease and disability. Despite the benefits of genetic testing, such as increased screening or prophylactic interventions, individuals at high risk for serious illness may become increasingly fearful or distressed about the future. In fact, a consistent finding is that the majority of individuals do adjust to genetic test results, however a subset of individuals undergoing genetic testing for Adult Onset Hereditary Disease (AOHD) experience psychological distress, such as anxiety or depressive symptoms. A screening tool, designed for the genetic testing context, would be helpful in assisting geneticists, genetic counselors or primary care providers to identify this particular group for the implementation of at appropriate preventive or follow-up interventions. Herein, we present a newly developed psychological risk screening instrument that can be readily used within a genetic service for AOHD.

Risk Factors and Psychological Impact of Genetic Testing: The Evidence

The knowledge of genetic risk is life-long and individuals and families often find themselves confronted with an ongoing need to face issues and make decisions. Examples include decision-making around prevention and treatment options (e.g. increased surveillance, prophylactic surgery, chemoprevention), the need to notify family members about a mutation in the family , and in personal decision-making, for example decisions involving childbearing [1, 2]. Studies utilizing standardized measures of distress (e.g. global measures of anxiety or depression symptoms) have demonstrated that 8 to 25% of individuals undergoing genetic testing experience distress, the level of which falls within the clinical ranges for depression and anxiety [2-5]. Studies that have utilized standardized measures of *distress-specific distress* (i.e.

instruments measuring breast/ovarian cancer worry) have demonstrated higher prevalence levels [6, 7].

The risk factors for psychological symptoms amongst individuals undergoing genetic testing have been delineated in several studies [4, 8, 9]. While there is generally elevated distress using global measures for depression or anxiety among those who receive positive test results [9-11], individuals testing negative or receiving uninformative results may also have adjustment difficulties [12] following testing. For example, individuals may feel guilt or continue to worry about their disease risk even when testing negative [2, 7, 12]. These findings highlight the importance of considering risk factors in addition to the type of test result itself. Individuals who have elevated psychological symptoms at the pre-test stage and those with a previous psychiatric history (i.e., depression) are particularly at risk for an adverse psychological outcome after testing [2, 8, 9].

Additional risk factors for distress are more specific to the genetics context and include the level of penetrance of the gene mutation or degree of certainty of developing the disease [4]. The perception of control over the disease (including the number of prevention/treatment options) and perception of the immediacy of risk (proximity in age to perceived disease onset) are important predictors [4, 13]. The expectation of a negative test result can play a role in adjustment, as can the context of test results of other family members [9, 14]. As in other medical areas, specific coping styles can affect adjustment [15]. The prior experiences with loss of family members to disease, as well as the developmental level (i.e. young age) of the individual at the time of the loss [2, 3, 16] are significant factors affecting potential adjustment. In addition, the prior experience of giving care to a family member with the disease and lower

levels of social support have been associated with poorer adjustment following a positive test result [2-4, 8, 16].

It is clear that there is not one predominant factor, but rather, a series of variables that can be assessed prior to receiving a test result that may contribute to elevated levels of psychological distress following genetic testing [2, 17]. Emotional reactions may impede the assimilation of risk information and the adoption of preventive measures recommended following notification of a mutation [2, 18]. Psychological distress occurs along a continuum [19, 20] and can be difficult to identify by health professionals [21]. Distress may not become manifest to the health care team until the patient reaches an observable crisis level, i.e. the onset of severe depression or anxiety, or significant conflicts with the family. An early screening instrument would enable healthcare providers to identify patients being at higher psychological risk in order that appropriate support can be given at the right time. In fact, there is now a general consensus that genetic testing should be accompanied by psychological support to promote optimal adjustment [2, 22].

Screening for Psychological Risk Factors- Why is it necessary?

The gold standard for identifying psychologically distressed individuals involves structured clinical interviews administered by a clinical psychologist or psychiatrist [21]. However, it is too costly and often not feasible in genetic clinics. Standardized measures of psychological functioning (e.g. global scales of depression or anxiety) can also be used as a method for identifying distress. However, few clinics use these measures in practice because of personnel and time requirements for scoring and interpretation of them. Furthermore, items on these measures typically focus on symptoms of anxiety or depression, rather than on variables

associated with heritable disease or genetic testing or risk, which may pose barriers for use by genetics health service providers who may prefer instruments that, at face value, appear to them and their patients as being clinically more relevant to the genetic testing context.

More recently, new outcome measures designed to assess the psychological impact of receiving genetic information have been developed. For example, the Multidimensional Impact of Cancer Risk Assessment (MICRA) is designed to assess concerns and impacts associated with genetic testing for BRCA1/2 [19] and another tool, the Psychological Adaptation to Genetic Information Scale, is now available [23]. While these measures will require further validation they provide more clinically relevant approaches to capturing specific impacts of genetic information, such as the increased sense of vulnerability often experienced following genetic testing [19, 23].

Measures of global psychological functioning and the evolving outcome measurement tools for the genetics field are not designed to "predict" vulnerability for future distress, but rather, measure current distress levels. Screening, the aim of the tool developed in this study in contrast, is a rapid, cost-effective alternative [21] to prospectively identify individuals who may experience significant difficulty in their attempts to adapt to their genetic information [17]. A screening tool enables providers to offer timely and focused educational and psychosocial interventions to *prevent* future distress.

The primary *objective* of this study was to develop a brief, reliable and valid psychological risk screening instrument for use in the genetic testing context. The new instrument aimed to incorporate empirically based risk factors for psychological symptoms and would need to show a high sensitivity, specificity and predictive validity indicating risk for future distress post genetic testing results. A cutoff point would need to be determined to guide

clinical decisions as to whether or not to refer, further assess, or intervene to reduce an individual's expressed concern.

METHODS AND MATERIALS

The study was carried out from September 2005 to July 2010, with research ethics board approval from participating genetics clinics: Toronto (Mount Sinai Hospital, North York General Hospital, Princess Margaret Hospital); Ottawa (Children's Hospital of Eastern Ontario); and Vancouver (British Columbia Cancer Agency). Individuals beginning the genetic testing process for AOHD at each site were approached by genetic counsellors on the project team for their permission to be contacted about the study. Those who expressed interest were mailed the baseline package that included the informed consent. The informed consent included all components of the study, including questionnaires, follow-up phone calls, telephone interviews, as well as to the release of their genetic testing information to the research team.

A two phase approach was used for this study**: *Phase I:*** *Item Generation and Refinement,* and ***Phase II:*** *Validation*. The multi-stage method [24] takes validation into consideration at each stage of scale development and has been used successfully in previous studies [25].

Phase I: Item Generation and Refinement.

Item generation

To generate items for the Genetic Psychosocial Risk Instrument (GPRI), a literature search was performed for the following AOHDs: Cancer (Hereditary Breast-Ovarian Cancer Syndrome/ Lynch Syndrome), Huntington Disease (HD), and Hemochromatosis. These diseases were selected as they represented the majority of patients attending genetic clinics and had an

associated available psychosocial literature for review. Databases including Cinahl (1982 to 2006), Medline (1966 to 2006), PsychInfo (1985 to 2006), and Pubmed (1985 to 2006) were searched as well as hand search of references from major publications. Keywords included: genetic screening, genetic testing, psychological, psychological well-being, psychological adjustment, stress, adaptation, cancer worry, disease worry, and distress. Selection criteria for the literature review included studies with a follow-up design or review articles. Each selected study was reviewed by two reviewers on its quality of evidence and generalizability using a standardized template. A total of 73 relevant studies were identified among the disease groups: 49 on cancer, 20 on HD, 2 on Hemochromatosis, and 2 described mixed conditions.

Risk factors for psychological distress identified by the literature review provided the basis for item generation. Items were written in a mixed format where respondents were asked for their endorsement of each statement ranging from Yes/No for risk factors of binary nature, to a 5-point likert-type scale for risk factors with stages in frequency and/or intensity. The instrument items were further refined by 10 genetic service providers (3 geneticists, 4 genetic counselors, 2 oncologists, 1 genetics nurse) rating items on *comprehension, readability, and perceived clinical relevance* using a ten-point scale with 0 being "excellent/definitely relevant" and 10 being "very poor/definitely not relevant". Risk factor items were removed if rated above five by more than 3 providers. Providers were also asked to suggest additional risk factor items. These suggestions were checked against the literature for empirical evidence. Following this step, 7 volunteers undergoing genetic testing for AOHDs were recruited to try out the scale for clarity, succinctness and relevance from the clients' perspectives. At this stage, the proposed instrument consisted of 56 items: demographics (4 items); perceived risk (8 items); life events and family history of the disease (8 items); perceived impact of carrying a mutation (9 items);

family communication (6 items); disease specific concerns (5 items); optimism (3 items); social support (3 items), pre-morbid functioning and previous psychiatric history (10 items).

Item refinement:

Subjects: Following informed consent, a convenient sample of 141 participants who had given blood for genetic tests at the Toronto and Ottawa sites completed the GPRI (using a three patients per item ratio) to select the best items for the candidate scale. The participants were middle aged (48.67 ± 13.29), mostly female (77%) testing for hereditary breast cancer, and many (65%) had already suffered the onset of the illness.

Scoring: To ensure that binary items carry an equal weight as the 5-point likert-type items, a score of 5 was assigned to *Yes* and 1 to *No.* A score of 3 or mean-substitute was assigned to *Not Applicable* to allow it to be counted in the total score. Reliability analysis was carried out and a Cronbach's Alpha was set for .75 or higher for the scale to move to the next phase [26]. Any item with an item-total correlation less than .20 was identified for potential removal. Using team consensus, a total of 19 items were removed, combined or substituted, resulting in a 37 item GPRI candidate scale at the end of phase I.

Phase II: Scale Validation

Subjects: Individuals undergoing genetic testing for one of the AOHDs in each of the five study sites were invited to participate: 1) age 18 or above undergoing genetic testing for cancer, HD, or Hemochromatosis; 2) fluent in English; and 3) residing within 1.5 hours driving distance from study site. Although the onset of an AOHD was not an exclusion criterion, individuals in advanced stages of the illness and / or who were unable to consent due to cognitive impairment

were excluded. At baseline, participants were asked to complete a set of self-report questionnaires (e.g. Brief Symptom Inventory, etc.) described below within a one month period following the provision of a blood sample. For those who received a genetic test result, questionnaires were mailed within two weeks to one month of the disclosure of test result. These participants were also telephoned to complete the Hamilton Depression and Hamilton telephone-based Anxiety Scales to further assess depressive and anxiety symptoms. .

Materials**:** At baseline, three psychosocial measures were used: *GPRI Candidate Scale* from Phase I. To facilitate scoring of the scale by genetic providers, scores for response to each item on the GPRI were imbedded in the questionnaire, where clinicians could calculate a total score in less than 5 minutes. *Brief Symptom Inventory* (BSI) The BSI is a 53-item measure of psychological distress that contains three global scales i) depression, ii) anxiety and iii) somatization [27]. While it has some limitations being a self-report measure it has been well-validated and widely used in medical and psychiatric populations to assess psychological functioning; *Impact of Event Scale (IES)*: The IES is a 15-item, likert-style scale used to assess the experience of a specific stress response and is designed to be easily anchored in relation to a specific stressor or life event. It has been extensively utilized in the genetics literature to assess genetic testing-related distress; we similarly anchored the IES items in relation to the anticipation of the genetic test result at baseline and in relation to the actual genetic test at follow- up . The IES has two sub-scales: i) intrusive thoughts and feelings associated with the stressful life event, and ii) items associated with patterns of avoidance of certain thoughts, feelings, or situations [28].

Measures at one month post genetic testing results included: the self -reports scales of the BSI, IES and each participant received a telephone call for the telephone-based Hamilton

Depression 29-item Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A). The HAM-D evaluates depressed mood, vegetative and cognitive symptoms of depression, and comorbid anxiety symptoms [29]. The HAM-A quantifies the severity of anxiety symptomatology and consists of 14 items. The HAM-D and HAM-A have demonstrated validity in clinical interview, in person or by telephone [30]. These two instruments were selected as main outcome measures based on the literature that the standardized interview based-rating scales should be used over subjective report scales as the principal outcome criterion in psychological distress both in general practice and in research trials [34]. Cases would be defined by established cut-offs from the literature for HAM-D >=12 [35] or HAM-A >=10 [36]. These cut off points were established for populations in general practice, which was our study population.

The one-month follow-up time point was selected as it is when elevated distress might occur [31]. In addition, the 2-week duration criterion for depression defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) is met by this time frame.

Assessing Psychometric Property of the Scale

As a first step, items were required to have at least an 80% response rate. Second, each item was examined to determine its contribution to the internal consistency of the total 37-item scale. The minimum item-total correlation was set at .20 [32].

A principal components factor analysis with varimax rotation was performed on the candidate scale to examine the factor structure and the loading of the items. To assess the *convergent validity* of the candidate scale, the correlations between baseline GPRI, IES and BSI were calculated. To assess the *sensitivity, specificity and predictive value* of the GPRI, the

follow-up HAM-D and HAM-A were used to identify "cases" who met cut offs for either the depression or anxiety symptomatology. For example, participants with a high GPRI at baseline would be classified as "at risk" for future onset of adjustment difficulties. This would be confirmed by a high HAM-D or HAM-A score or "case" during 1 month follow-up. Similarly, those with a low GPRI score should receive low score in HAM-D or HAM-A as "non-cases". The predictive value of the GRPI, describing the number of test-positives (in our case, high GPRI) who truly have the psychological condition (i.e. cases identified by HAM-D or HAM-A), was tested by a Receiver Operating Characteristic (ROC) curve which visually plotted the true positive rate (sensitivity) over false positive rate (1-specificity). We included cases to be identified by either anxiety and/or depressive symptomatology as both have been reported in the literature [8, 9].

To address the issue of missing follow-up data in a cohort study, as suggested in the literature [33], we tested the assumption that the sub sample with missing data had a similar baseline exposure (similar GPRI) as the non-missing subsample by comparing baseline GPRI between the participants and dropouts. This step assesses if there was systematic bias resulting from the loss of information in the follow-up period.

RESULTS

Participant characteristics

Study packages were mailed to 1129 individuals interested in hearing more about the study. Of these individuals, 722 of them consented and 712 (98%) completed the GPRI. Most participants were tested for the inheritable cancers, while a small percentage of participants were tested for

hemochromatosis and HD. Similar to phase I, phase II participants were mostly female, at mid-life stage, and more than half had a past diagnosis of the disease (see table 1).

Insert Table 1 about Here

Of the 712 participants, 85 (12%) did not receive genetic testing results at the scheduled follow-up time and were not eligible for follow-up measures on psychological symptoms in response to a genetic testing result. Of the remaining 627 participants, 152 (24%) did not return the self-administered follow-up questionnaires and 12 (2%) submitted the follow-up questionnaire package but did not complete a standardized telephone interview using HAM-D and HAM-A (up to 4 telephone calls were made to reach each participant). Therefore the final number of participants with complete follow-up data is 463 (74%). The age, and baseline GPRI score between individuals who did not receive genetic testing results (age 51.4±12.7, GPRI 49.3±12.7), those who did not return the follow-up questionnaires (age 48.1±11.6, GPRI 50.2±14.4) and those who completed follow-up measures (age 50.1±12.8, GPRI 49.1±13.5) were compared. There was no statistically significant group difference (ANOVA and all post-hoc comparisons $p>0.05$).

Because of the similarity between the dropouts and completers, we proceeded with reliability and validity analysis of the tool using the subsample that provided outcome data.

We carried out the calculations for distress level, for example, for depression and anxiety symptoms using the BSI data, for specific distress associated a genetic test result using the IES. Approximately, 13.0% to 20.1% of participants reached the threshold of moderate to severe distress respectively (see table 2).

Insert Table 2 about Here

HAM-D and HAM-A interview data from 463 participants were used as a further validation tool to measure psychological symptoms post genetic testing results. Defined by cut-offs for HAM-D >=12 [35] or HAM-A >=10 in the literature [36], the rates for psychological distress of either depression or anxiety was 13.7% (N=63). The rate was 13% for HD, 15% for breast cancer and 7% for Lynch Syndrome.

Reliability and Factor Analysis

A reliability analysis was performed on 37 items. Twenty items belonging to 18 questions were selected based on the criteria for item selection described in the methods section. The Cronbach's alpha of the 20 item GPRI was 0.81 suggesting a good level of internal consistency.

The factor analysis resulted in a psychometrically sound 3-factor solution, with subscales representing the dimensions of: 1) *Perceived impact and personal adjustment to genetic testing* (12 items); 2) *Past history of mental health concerns* (5 items) and 3) *Personal history/family history/loss to cancer* (3 items). All three factors met the minimum Eigenvalue criteria of 1.

The first, 12-item factor (ALPHA = 0.85), accounting for 22% of the variance, includes items associated with the anticipated or experienced impact of being at high risk for AOHD. Example items included: "My worries about the disease affect my daily mood"; "The disease for which I am at risk is currently causing a significant disruption in my family life".

The second 5-item factor (ALPHA = 0.76), accounted for an additional 14% of the total variance, and reflected a sense of a person's past history or vulnerability in the area of mental health , e.g. "I have had emotional problems in the past", These items have been used in other medical health areas [37, 38] and tend to be predictive of maladjustment [20] following a life event.

The third 3 item factor (ALPHA = 0.08), accounted for 8% of the total variance and pertained to personal or family-related experiences associated with the hereditable disorder for which the participant is undergoing testing. . Examples include: "I have a personal diagnosis of the disease for which I am receiving counseling"; "I lost a close family member to the disease for which I am receiving counseling"; and "I have taken care of a very ill parent or another close family member". These 3 final items had low item total correlation because they were different from the rest of the items in that they focused on direct experiences related to the illness, rather than psychosocial-related items. These items were kept in the scale as they contributed significantly to the overall variance, and correlated highly with HAM-D and HAM-A. To determine the relationships between the three factors/subscales, correlations were computed. Factor1 and factor2 had moderate correlations with each other (factor1/factor2 $r=0.30$, $p<0.01$). The correlation of the first two factors with factor3 was much lower as expected (factor1/factor3 $r=0.06$, and factor2/factor3 $r=0.01$, not statistically significant). These results support the multidimensional character of the GPRI scale (see Table 3).

Insert Table 3 about Here

One additional statement "I am interested in talking to a counselor about one or more of these concerns" was added to the tool at the end as suggested by participants and providers to remind them the option of seeing a counselor if required. This statement is not part of the items examined during the instrument development and therefore does not carry a score.

The total score for the 20 item GPRI ranged from 20 to 100, with a sample mean 49.36 ± 13.23. The total was calculated by the sum of the raw scores for each of the statements. Females had a significantly higher score for the GPRI than males (50.37 ± 13.14 vs. 41.91 ± 11.47,

p<0.01), and participants testing for HD had a higher, but non-significant score than participants testing for cancer (52.24±13.24 vs. 49.37±13.22, n.s.).

Validity

Construct validity – correlations: The GPRI was assessed for its correlation with other standardized self-report measures of psychological functioning collected at baseline. Convergent validity was demonstrated by the correlation between the GPRI and the following measures: a positive correlation with the IES total score at r = .51, p< .001, and with BSI at r = .58, p< .001.

Sensitivity, specificity and the predictive value of GPRI for future distress: The telephone interview-based HAM-D and HAM-A were used to identify subjects who presented specific psychological symptoms of distress such as depression and/or anxiety during the one month post genetic testing follow-up. A total of 63 "cases" (13.6% of 463 completers) were identified as having psychological distress levels above specified thresholds defined in the methods section for either anxiety or depression symptoms or both. About 23% among participants testing positive met the distress threshold, as did 10% among those with negative results, and 20% among uninformative. Participants scoring above HAM-D (N=55) threshold had significantly higher GPRI scores than participants below the threshold (N=408) (61.12±13.27 vs. 47.91±12.27, p<0.01). Same patterns were observed for HAM-A high (N=40) vs. low (N=423) (62.53±12.92 vs. 48.25± 12.43, p<0.01).

Other demographic characteristics of these 63 subjects include: most were female and undergoing testing for BRCA1/2, which was similar to the whole sample of 712 (table 1). Compared with the whole sample, these subjects had a slightly higher percentage of personal history of cancer (65% vs. 62%), higher rate of recent significant event of loss (56% vs. 47%), greater percentage reporting disease worries affecting mood (54.8% vs. 27%), having a feeling of

sadness in the past month (46% vs. 17%) and anxiousness in the past month (33% vs. 17%). Our instrument captured all of these characteristics of this subsample.

The predictive value of a test describes how many of the test-positives (in this case, a high score on GPRI) truly have the psychological condition. An ROC curve was used to plot the true positive rate (sensitivity) over the false positive rate (1-specificity). A good ROC curve rises sharply, indicating a high proportion in true positive and a low proportion of false positives. The ROC curve for the GPRI was 0.78, which is considered as an indicator of an adequate screening instrument [39].

An important purpose of the GRPI in our study was to identify individuals at risk for post genetic testing psychological distress. Therefore, the cutoff value was set to maximize sensitivity – in another word, not to miss detecting a "case". Using a GPRI cut off score of 50, the instrument was able to predict 84% of the "cases" identified by HAM-D or HAM-A conducted post genetic testing results, with a specificity value of 60% (Figure 1).

Insert Figure 1 about Here

DISCUSSION

The aim of this study was to develop a brief, easy-to-use psychosocial screening instrument specific for the genetic testing context and to examine its reliability and validity (Appendix A). To our knowledge this is the first report of a psychosocial screening instrument for use across AOHD. Unlike current psychological instruments used mainly in research studies in genetics clinics to identify existing global symptoms of depression and anxiety, or impacts, the GPRI assesses *psychological risk factors*, such as the specific anticipated impacts of a genetic testing result and the perception of the disease. The GPRI demonstrates promising psychometric

properties as a tool designed to assist genetics health care providers determine which of their patients undergoing genetic testing for AOHD is at increased psychological risk and should likely be considered for additional psychosocial support to facilitate adjustment to a test result.

A high reliability was demonstrated by a Cronbach's Alpha at 0.81, moderate to high item-total correlation and inter-item correlation of the whole scale. The construct validity of the scale was supported by high correlations between the GPRI and standardized psychological measures (BSI, IES). The clinical utility and predictive value of the GPRI was supported as well. A GPRI score above the cutoff of 50 at baseline was able to predict 84% of "distress" cases identified by HAM-D or HAM-A, a strong indicator of its potential usefulness in a clinical setting.

A brief self-administered screening tool will be easy and likely highly acceptable for incorporation into genetics clinics. The GPRI can be completed and scored quickly during clinical visits and without additional burden to patients and health providers. In addition, by focusing specifically on known risk factors associated with inheritable illness, the instrument will be perceived as being more clinically relevant and acceptable to patients. Patients with higher GPRI scores can be flagged and either receive telephone follow-up to further assess concerns or potential distress or be invited back for an appointment for further assessment and required psychological treatment.

Alternatively, genetic clinics with available psychosocial personnel could utilize the tool to guide referrals for a formal psychosocial assessment that can further explore and address specific self-reported psychological factors. For example, in the case where an individual is particularly fearful of developing an illness or is concerned about specific impacts, such as expecting relationship or family communications difficulties, information on communication

strategies, personal coaching or family–based interventions could be employed to support the individual. For an individuals who reports a past history of psychological illness, a mental health professional could further assess current psychological functioning and implement specific approaches, and could offer cognitive-behavioral strategies or psychotropic medication to assist in the management of anxiety or depressive symptoms [40]. Several items incorporate variables related to heritable disease experiences and associated perceptions which can be used to guide educational interventions to correct any myths or beliefs.

The scale appeared highly acceptable to patients. A high face validity will contribute to better scale uptake being perceived as "user friendly" and clinically relevant, compared for example, to a standardized psychological instrument on depression, which have demonstrated some barriers to clinic uptake [19]. The GPRI in contrast might be considered as a "communimetric measure", that is, the items themselves are useful for the clinician in communicating concerns about specific areas of functioning directly with the patient [41].

Left untreated, significant levels of psychological symptoms may lead to lower quality of life [40], and lower satisfaction with genetics services [21]. A psychological screening approach allows both for careful monitoring during a known stressful period-that of awaiting test results [42], and provides an opportunity for any planned follow-up care. Flagging those individuals who might benefit most from psychosocial care also best utilizes the often limited psychological resources in genetic clinics [2, 20, 21].

Our study findings are limited by the characteristics of the sample, in that most participants were female and undergoing testing for *BRCA1/2*. This pattern is similar to that observed in the literature on genetic testing for AOHD, which is predominantly focused on Hereditary Breast-Ovarian Cancer Syndrome. We attempted to obtain a larger sample of

individuals undergoing genetic testing for HD or Lynch Syndrome which would presumably provide a greater sample of males. However, these sample pools were much smaller. However, this study and the resulting GPRI represent an attempt to begin the development of a general tool that addresses concerns that are relevant across genetic samples. Our belief stemming from clinical practice and the associated literature suggest that the identified mental health issues or adjustment risk factors are not disease specific. We suggest that future studies further address the validity of GPRI in male populations and in the rare adult onset hereditary diseases, such as HD. Future studies should also include randomized controlled trials to assess the effectiveness of the GPRI in predicting distress, its impact on referral patterns, patient and provider satisfaction, as well as on cost-effectiveness. The GPRI could also be evaluated in primary care settings where genetics services might be offered more frequently to meet the demand.

CONCLUSIONS

This is the first study to develop a screening tool specifically to help identify individuals undergoing genetic testing for AOHD who are at increased psychological risk. The study resulted in an easy to use, 20-item scale consisting of 3 factors with promising psychometric properties. The GPRI has the potential to be used as a clinical screening tool and as a validated measure for future studies. Future work can examine its impact on clinical referral patterns within the field of genetics, and on its acceptability, reliability and validity with larger samples of individuals undergoing genetic testing for HD, Lynch Syndrome, and potentially for emerging new genetic tests, such as for cardiac or psychiatric disorders.

Acknowledgement

The first author is a recipient of a career scientist award from the Canadian Institutes of Health Research (CIHR) and the Ontario Women's Health Council. This study was funded by Canadian Institutes of Health Research (CIHR) Grant No. AHC 73144. We would like to express our gratitude to all the genetic testing patients who participated in our study. Thank you for your contribution towards this very important work and the development of the instrument. Thank you also to the genetic counselors and clinic staff from the participating genetic centers who assisted in recruitment: Children's Hospital of Eastern Ontario (Eastern Ontario Regional Genetics Centre); North York General Hospital (Clinical Genetics); Mount Sinai Hospital (Familial GI Cancer Registry & Familial Breast Cancer Clinic); Princess Margaret Hospital (Familial Breast & Ovarian Cancer Clinic); and BC Cancer Agency (Hereditary Cancer Program). We would also like to thank the research staff for their commitment and hard work to complete this national multi-site study. Finally, the team would like to pay special recognition to the late Dr. Anne Summers, who was co-investigator on the team. Her dedication to the need for empirically based tools and her strong vision to support recipients of new genetic technology were key influences in the conceptualization, funding and completion of this study.

Ethics: Research Ethics Board approval was obtained at all five participating sites: Toronto (Mount Sinai Hospital, North York General Hospital, Princess Margaret Hospital); Ottawa (Children's Hospital of Eastern Ontario); and Vancouver (British Columbia Cancer Agency).

Data Sharing Statement: There is no additional data available

Conflict of Interest: The authors do not have any conflict of interest to disclose.

Funding: This study was funded by Canadian Institutes of Health Research (CIHR) Grant No. AHC 73144.

Contributorship Statements

Dr. Mary Jane Esplen

Principal Applicant responsible for leading all aspects of the research, oversees budget, hiring staff, supervising data collection, analysis and interpretation, and writing of all manuscripts and reports.

Dr. Mario Cappelli

Co-principal inv. responsible for assisting in item generation and refinement, the implementation of data collection, interpretation of findings and writing of manuscripts and reports.

Dr. Jiahui Wong

Co- Applicant responsible assisting in instrument development, statistical procedures, sampling and interpretation of findings and writing of manuscripts and reports.

Dr. Joan Bottorff

Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services, development of guidelines and writing of manuscripts and reports.

Dr. Jon Hunter

Co-Applicant responsible for assisting in item generation and refinement, guideline development, interpretation of findings and writing of manuscripts and reports.

Dr. June Carroll

Co-Applicant responsible for assisting in item generation and refinement, implementation of the screening validation strategy and development of guidelines, interpretation of findings and writing of manuscripts and reports.

Dr. Michel Dorval

Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services, interpretation of findings and writing of manuscripts and reports.

Dr. Brenda Wilson

Co-Applicant responsible for co-leading the implementation of the consensus guidelines components of the proposed study. Will assist in item generation for tool, interpretation of findings, writing of manuscripts and reports.

Dr. Judith Allanson

Co-Applicant responsible for refining of items, guiding the recruitment of providers/patients and testing of the instrument in genetic services, development of guidelines and writing of manuscripts and reports.

Ms. Kara Semotiuk

Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services and development of guidelines, and writing of manuscripts and reports.

Ms. Melyssa Aronson

Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services, development of guidelines and writing of manuscripts and reports.

Dr. Louise Bordeleau

Co-Applicant responsible for overseeing recruitment at MSH and UHN site in Toronto, testing of instrument and interpretation of findings, writing of manuscripts and reports.

Ms. Nicole Charlemagne

Project coordinator, responsible for: patient recruitment and follow-up; assisting in item generation, refinement, and overall layout and design of tool; data collection, data entry, and data clean-up; revisions and submission of manuscript.

Dr. Wendy Meschino

Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services, interpretation of findings and writing of manuscripts and reports.

REFERENCES

1. Lerman C, Croyle RT. Emotional and behavioral responses to genetic testing for susceptibility to cancer. *Oncology (Williston Park)*. 1996;**10**:191-5, 9; discussion 200-2.

2. Bleiker EM, Hahn DE, Aaronson NK. Psychosocial issues in cancer genetics--current status and future directions. *Acta Oncol*. 2003;**42**:276-86.

3. Wellisch DK, Lindberg NM. A psychological profile of depressed and nondepressed women at high risk for breast cancer. *Psychosomatics*. 2001;**42**:330-6.

4. Broadstock M, Michie S, Marteau T. Psychological consequences of predictive genetic testing: a systematic review. *Eur J Hum Genet*. 2000;**8**:731-8.

5. Ho SM, Ho JW, Bonanno GA, et al. Hopefulness predicts resilience after hereditary colorectal cancer genetic testing: a prospective outcome trajectories study. *BMC Cancer*. 2010;**10**:279.

6. Trask PC, Paterson AG, Wang C, et al. Cancer-specific worry interference in women attending a breast and ovarian cancer risk evaluation program: impact on emotional distress and health functioning. *Psychooncology*. 2001;**10**:349-60.

7. Coyne JC, Kruus L, Racioppo M, et al. What do ratings of cancer-specific distress mean among women at high risk of breast and ovarian cancer? *Am J Med Genet A*. 2003;**116A**:222-8.

8. Marteau TM, Croyle RT. The new genetics. Psychological responses to genetic testing. *BMJ*. 1998;**316**:693-6.

9. Meiser B. Psychological impact of genetic testing for cancer susceptibility: an update of the literature. *Psychooncology*. 2005;**14**:1060-74.

10. Hamilton JG, Lobel M, Moyer A. Emotional distress following genetic testing for hereditary breast and ovarian cancer: a meta-analytic review. *Health Psychol*. 2009;**28**:510-8.

11. Shaw C, Abrams K, Marteau TM. Psychological impact of predicting individuals' risks of illness: a systematic review. *Soc Sci Med*. 1999;**49**:1571-98.

12. Dorval M, Gauthier G, Maunsell E, et al. No evidence of false reassurance among women with an inconclusive BRCA1/2 genetic test result. *Cancer Epidemiol Biomarkers Prev*. 2005;**14**:2862-7.

13. Cameron LD, Sherman KA, Marteau TM, et al. Impact of genetic risk information and type of disease on perceived risk, anticipated affect, and expected consequences of genetic tests. *Health Psychol*. 2009;**28**:307-16.

14. Smith KR, West JA, Croyle RT, et al. Familial context of genetic testing for cancer susceptibility: moderating effect of siblings' test results on psychological distress one to two weeks after BRCA1 mutation testing. *Cancer Epidemiol Biomarkers Prev*. 1999;**8**:385-92.

15. Dougall AL, Smith AW, Somers TJ, et al. Coping with genetic testing for breast cancer susceptibility. *Psychosom Med*. 2009;**71**:98-105.

16. Esplen MJ, Urquhart C, Butler K, et al. The experience of loss and anticipation of distress in colorectal cancer patients undergoing genetic testing. *J Psychosom Res*. 2003;**55**:427-35.

17. Zabora JR. Screening procedures for psychological distress. In: Holland JC, editor. Psycho-Oncology. New York: Oxford University Press; 1998. p. 653-62.

18. Watson M, Lloyd S, Davidson J, et al. The impact of genetic counselling on risk perception and mental health in women with a family history of breast cancer. *Br J Cancer*. 1999;**79**:868-74.

19. Cella D, Hughes C, Peterman A, et al. A brief assessment of concerns associated with genetic testing for cancer: the Multidimensional Impact of Cancer Risk Assessment (MICRA) questionnaire. *Health Psychol*. 2002;**21**:564-72.

20. Zabora J, BrintzenhofeSzoc K, Curbow B, et al. The prevalence of psychological distress by cancer site. *Psychooncology*. 2001;**10**:19-28.

21. Thewes B, Meiser B, Tucker K, et al. Screening for psychological distress and vulnerability factors in women at increased risk for breast cancer: A review of the literature. *Psychology, Health & Medicine*. 2003;**8**:289-303.

22. Howell D, Keller-Olaman S, Oliver T, et al. A Pan-Canadian Practice Guideline: Screening, Assessment and Care of Psychosocial Distress (Depression, Anxiety) in Adults with

Cancer. Toronto: Canadian Partnership Against Cancer (Cancer Journey Action Group) and the Canadian Association of Psychosocial Oncology2010.

23. Read CY, Perry DJ, Duffy ME. Design and psychometric evaluation of the Psychological Adaptation to Genetic Information Scale. *J Nurs Scholarsh*. 2005;**37**:203-8.

24. Jackson D. A sequential system for personality scale development. In: Spielberger C, editor. Current Topics in Clinical and Community Psychology. New York: Academic Press; 1970. p. 61-96.

25. Stuckless N, Goranson R. The vengeance scale: Development of a measure of attitudes toward revenge. *Journal of Social Behavior and Personality*. 1992;**7**:25-42.

26. Briggs SR, Cheek JM. The role of factor analysis in the development and evaluation of personality scales. *Journal of Personality*. 1986;**54**:106-48.

27. Derogatis LR. The brief symptom inventory (BSI). Administration, Scoring and Procedures Manual. 3rd ed. New York: National Computer Systems; 1993.

28. Horowitz MJ, Wilner N, Alvarez W. Impact of Events Scale: A Measure of Subjective Stress. *Psychosomatic Medicine*. 1979;**41**:209-18.

29. Hamilton MA. A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*. 1960;**23**:56-23.

30. Katzelnick DJ, Simon GE, Pearson SD, et al. Randomized trial of a depression management program in high utilizers of medical care. *Arch Fam Med*. 2000;**9**:345-51.

31. DudokdeWit AC, Tibben A, Duivenvoorden HJ, et al. Predicting adaptation to presymptomatic DNA testing for late onset disorders: who will experience distress? Rotterdam Leiden Genetics Workgroup. *J Med Genet*. 1998;**35**:745-54.

32. Walsh W, Betz N. Tests and Assessments. New Jersey: Prentice Hall Inc; 1985.

33. Melnick EL, Everitt BS. Quantitative risk analysis and assessment. Hebokea NJ: John Wiley & Sons; 2008.

34. Moller HJ. Rating depressed patients: observer- vs self-assessment. *Eur Psychiatry*. 2000;**15**:160-72.

35. Aben I, Verhey F, Lousberg R, et al. Validity of the beck depression inventory, hospital anxiety and depression scale, SCL-90, and hamilton depression rating scale as screening instruments for depression in stroke patients. *Psychosomatics*. 2002;**43**:386-93.

36. Pasquini M, Biondi M, Costantini A, et al. Detection and treatment of depressive and anxiety disorders among cancer patients: feasibility and preliminary findings from a liaison service in an oncology division. *Depress Anxiety*. 2006;**23**:441-8.

37. Beck CT. A checklist to identify women at risk for developing postpartum depression. *J Obstet Gynecol Neonatal Nurs*. 1998;**27**:39-46.

38. Reid AJ, Biringer A, Carroll JD, et al. Using the ALPHA form in practice to assess antenatal psychosocial health. Antenatal Psychosocial Health Assessment. *CMAJ*. 1998;**159**:677-84.

39. Goutham R. What is an ROC curve? *The Journal of Family Practice*. 2003;**52**:695.

40. Esplen MJ, Hunter J. Therapy in the Setting of Genetic Predisposition to Cancer' in 'Handbook of Psychotherapy in Cancer Care. In: Watson M, Kissane D, editors. Handbook of Psychotherapy in Cancer Care. London: John Wiley & Sons Ltd; 2011. p. 201-12.

41. Lyons JS. A Communication Theory of Measurement in Human Service Settings. New York: Springer; 2009.

42. Broadstock M, Michie S, Gray J, et al. The psychological consequences of offering mutation searching in the family for those at risk of hereditary breast and ovarian cancer--a pilot study. *Psychooncology*. 2000;**9**:537-48.

Title

Developing A Brief Screening Instrument for Psychosocial Risk Associated with Genetic Testing – A Pan Canadian Cohort Study

Corresponding Author Address

Mary Jane Esplen, PhD
CIHR Scientist and Professor
Department of Psychiatry, Faculty of Medicine, University of Toronto
Behavioral Sciences and Health Research Division
University Health Network
200 Elizabeth Street, 9-EN-242A
Toronto ON M5G 2C4 Canada
Tel: (416) 340-3024
Fax: (416) 340-4739
Email: mesplen@uhnres.utoronto.ca

List of Authors and Institutions

Mary Jane Esplen PhD[1,2,3], Mario Cappelli PhD[4], Jiahui Wong PhD[2,3], Joan Bottorff PhD[5], Jon Hunter MD[2,6], June Carroll MD[6], Michel Dorval PhD[7], Brenda Wilson PhD[8], Judith Allanson MD[9], Kara Semotiuk MSc[10], Melyssa Aronson MSc[10], Louise Bordeleau MD[11], Nicole Charlemagne MSW[1], Wendy Meschino MD[12]

[1]University Health Network, Toronto ON; [2]University of Toronto: Department of Psychiatry, Toronto ON; [3]de Souza Institute, Toronto ON; [4]Children's Hospital of Eastern Ontario, Ottawa ON; [5]University of British Columbia Okanagan, Kelowna BC; [6]Mount Sinai Hospital, Toronto ON; [7]Laval University, Quebec QC; [8]University of Ottawa, Ottawa ON; [9]Eastern Ontario Regional Genetics Centre, Ottawa ON; [10]Zane Cohen Centre for Digestive Diseases, Mount Sinai Hospital, Toronto ON; [11]McMaster University, Hamilton ON; [12]North York General Hospital, Toronto ON.

Keywords:

Genetics, Psychosocial, Screening, Psychosocial Problems, Psychosocial Functioning, Psychological Risk Factors

Word Count: 5124

Abstract:

Objectives: To develop a brief, reliable and valid instrument to screen psychosocial risk among those who are undergoing genetic testing for Adult-Onset Hereditary Disease (AOHD).

Design: A prospective two-phase cohort study.

Setting: 5 genetic testing centres for AOHD such as cancer, Huntingtons, or Hemochromatosis, in ambulatory clinics of tertiary hospitals across Canada.

Participants: 141 individuals undergoing genetic testing were approached and consented to the instrument development phase of the study (Phase I). The Genetic Psychosocial Risk Instrument (GPRI) developed in Phase I was tested in Phase II for item refinement and validation. A separate cohort of 722 individuals consented to the study, 712 completed the baseline package, and 463 completed all follow-up assessments. Most participants were female, at mid-life stage. Individuals in advanced stages of the illness or with cognitive impairment or language barrier were excluded.

Interventions: Phase I: GPRI items were generated from 1) a review of the literature, 2) input from genetic counselors and 3) phase I participants. Phase II: further item refinement and validation was conducted with a second cohort of participants who completed the GPRI at baseline and were followed for psychological distress one month post genetic testing results.

Primary and secondary outcome measures: GPRI, Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), Brief Symptom Inventory (BSI), and Impact of Event Scale (IES).

Results: The final 20 item GPRI had a high reliability - Cronbach's Alpha at 0.81. The construct validity was supported by high correlations between GPRI and BSI and IES. The predictive value was demonstrated by a Receiver Operating Characteristic (ROC) curve of 0.78 plotting GPRI against follow-up assessments using HAM-D and HAM-A.

Conclusions: With a cut off score of 50, GPRI identified 84% of participants who displayed distress post genetic testing results, supporting its potential usefulness in a clinical setting.

Word count: 299
Trial registration: Not applicable

Summary

1) Article Focus

- A significant group of individuals undergoing genetic testing for Adult onset disease experience distress or challenges in adaptation, some might develop depression or anxiety
- Existing psychological screening tools do not take into consideration "risk factors" associated with heritable illness or genetic-related stressors
- A screening tool designed for genetic testing services is a useful tool to guide clinicians in relation to which patients would benefit from added psychosocial support during the genetic testing process.

2) Key Messages

- A subgroup of patients undergoing genetic testing required added psychosocial support to facilitate adaptation to genetic/ risk information. Busy genetic service providers can face challenges to identify these individuals and provide timely interventions or referrals.
- A new brief instrument was designed and validated to identify those individuals at risk for psychological distress such as depression or anxiety who are undergoing genetic testing for adult onset diseases.
- This is the first study to develop and validate a psychological screening instrument for genetic testing field.

3) Strengths and Limitations

- This newly developed tool, Genetic Psychosocial Risk Instrument (GPRI), is the first reported psychosocial screening instrument for use across Adult Onset Hereditary Diseases.
- The GPRI demonstrates promising psychometric properties as a tool designed to assist genetics health care providers determine which of their patients undergoing genetic testing for AOHD is at increased psychological risk and who will benefit from added psychosocial support.
- Study findings are limited by the characteristics of the sample, most participants were female and undergoing testing for BRCA1/2. Future studies could further address the validity of GPRI in male populations and in the rare adult onset hereditary diseases, such as Huntington's disease.

INTRODUCTION

Genetic predisposition is an important determinant of chronic disease and disability. Despite the benefits of genetic testing, such as increased screening or prophylactic interventions, individuals at high risk for serious illness may become increasingly fearful or distressed about the future. In fact, a consistent finding is that the majority of individuals do adjust to genetic test results, however a subset of individuals undergoing genetic testing for Adult Onset Hereditary Disease (AOHD) experience psychological distress, such as anxiety or depressive symptoms. A screening tool, designed for the genetic testing context, would be helpful in assisting geneticists, genetic counselors or primary care providers to identify this particular group for the implementation of at appropriate preventive or follow-up interventions. Herein, we present a newly developed psychological risk screening instrument that can be readily used within a genetic service for AOHD.

Risk Factors and Psychological Impact of Genetic Testing: The Evidence

The knowledge of genetic risk is life-long and individuals and families often find themselves confronted with an ongoing need to face issues and make decisions. Examples include decision-making around prevention and treatment options (e.g. increased surveillance, prophylactic surgery, chemoprevention), the need to notify family members about a mutation in the family , and in personal decision-making, for example decisions involving childbearing [1, 2]. Studies utilizing standardized measures of distress (e.g. global measures of anxiety or depression symptoms) have demonstrated that 8 to 25% of individuals undergoing genetic testing experience distress, the level of which falls within the clinical ranges for depression and anxiety [2-5]. Studies that have utilized standardized measures of *distress-specific distress* (i.e.

instruments measuring breast/ovarian cancer worry) have demonstrated higher prevalence levels [6, 7].

The risk factors for psychological symptoms amongst individuals undergoing genetic testing have been delineated in several studies [4, 8, 9]. While there is generally elevated distress using global measures for depression or anxiety among those who receive positive test results [9-11], individuals testing negative or receiving uninformative results may also have adjustment difficulties [12] following testing. For example, individuals may feel guilt or continue to worry about their disease risk even when testing negative [2, 7, 12]. These findings highlight the importance of considering risk factors in addition to the type of test result itself. Individuals who have elevated psychological symptoms at the pre-test stage and those with a previous psychiatric history (i.e., depression) are particularly at risk for an adverse psychological outcome after testing [2, 8, 9].

Additional risk factors for distress are more specific to the genetics context and include the level of penetrance of the gene mutation or degree of certainty of developing the disease [4]. The perception of control over the disease (including the number of prevention/treatment options) and perception of the immediacy of risk (proximity in age to perceived disease onset) are important predictors [4, 13]. The expectation of a negative test result can play a role in adjustment, as can the context of test results of other family members [9, 14]. As in other medical areas, specific coping styles can affect adjustment [15]. The prior experiences with loss of family members to disease, as well as the developmental level (i.e. young age) of the individual at the time of the loss [2, 3, 16] are significant factors affecting potential adjustment. In addition, the prior experience of giving care to a family member with the disease and lower

levels of social support have been associated with poorer adjustment following a positive test result [2-4, 8, 16].

It is clear that there is not one predominant factor, but rather, a series of variables that can be assessed prior to receiving a test result that may contribute to elevated levels of psychological distress following genetic testing [2, 17]. Emotional reactions may impede the assimilation of risk information and the adoption of preventive measures recommended following notification of a mutation [2, 18]. Psychological distress occurs along a continuum [19, 20] and can be difficult to identify by health professionals [21]. Distress may not become manifest to the health care team until the patient reaches an observable crisis level, i.e. the onset of severe depression or anxiety, or significant conflicts with the family. An early screening instrument would enable healthcare providers to identify patients being at higher psychological risk in order that appropriate support can be given at the right time. In fact, there is now a general consensus that genetic testing should be accompanied by psychological support to promote optimal adjustment [2, 22].

Screening for Psychological Risk Factors- Why is it necessary?

The gold standard for identifying psychologically distressed individuals involves structured clinical interviews administered by a clinical psychologist or psychiatrist [21]. However, it is too costly and often not feasible in genetic clinics. Standardized measures of psychological functioning (e.g. global scales of depression or anxiety) can also be used as a method for identifying distress. However, few clinics use these measures in practice because of personnel and time requirements for scoring and interpretation of them. Furthermore, items on these measures typically focus on symptoms of anxiety or depression, rather than on variables

associated with heritable disease or genetic testing or risk, which may pose barriers for use by genetics health service providers who may prefer instruments that, at face value, appear to them and their patients as being clinically more relevant to the genetic testing context.

More recently, new outcome measures designed to assess the psychological impact of receiving genetic information have been developed. For example, the Multidimensional Impact of Cancer Risk Assessment (MICRA) is designed to assess concerns and impacts associated with genetic testing for BRCA1/2 [19] and another tool, the Psychological Adaptation to Genetic Information Scale, is now available [23]. While these measures will require further validation they provide more clinically relevant approaches to capturing specific impacts of genetic information, such as the increased sense of vulnerability often experienced following genetic testing [19, 23].

Measures of global psychological functioning and the evolving outcome measurement tools for the genetics field are not designed to "predict" vulnerability for future distress, but rather, measure current distress levels. Screening, the aim of the tool developed in this study in contrast, is a rapid, cost-effective alternative [21] to prospectively identify individuals who may experience significant difficulty in their attempts to adapt to their genetic information [17]. A screening tool enables providers to offer timely and focused educational and psychosocial interventions to *prevent* future distress.

The primary *objective* of this study was to develop a brief, reliable and valid psychological risk screening instrument for use in the genetic testing context. The new instrument aimed to incorporate empirically based risk factors for psychological symptoms and would need to show a high sensitivity, specificity and predictive validity indicating risk for future distress post genetic testing results. A cutoff point would need to be determined to guide

clinical decisions as to whether or not to refer, further assess, or intervene to reduce an individual's expressed concern.

METHODS AND MATERIALS

The study was carried out from September 2005 to July 2010, with research ethics board approval from participating genetics clinics: Toronto (Mount Sinai Hospital, North York General Hospital, Princess Margaret Hospital); Ottawa (Children's Hospital of Eastern Ontario); and Vancouver (British Columbia Cancer Agency). Individuals beginning the genetic testing process for AOHD at each site were approached by genetic counsellors on the project team for their permission to be contacted about the study. Those who expressed interest were mailed the baseline package that included the informed consent. The informed consent included all components of the study, including questionnaires, follow-up phone calls, telephone interviews, as well as to the release of their genetic testing information to the research team.

A two phase approach was used for this study**: *Phase I:*** *Item Generation and Refinement,* and ***Phase II:*** *Validation*. The multi-stage method [24] takes validation into consideration at each stage of scale development and has been used successfully in previous studies [25].

Phase I: Item Generation and Refinement.

Item generation

To generate items for the Genetic Psychosocial Risk Instrument (GPRI), a literature search was performed for the following AOHDs: Cancer (Hereditary Breast-Ovarian Cancer Syndrome/ Lynch Syndrome), Huntington Disease (HD), and Hemochromatosis. These diseases were selected as they represented the majority of patients attending genetic clinics and had an

associated available psychosocial literature for review. Databases including Cinahl (1982 to 2006), Medline (1966 to 2006), PsychInfo (1985 to 2006), and Pubmed (1985 to 2006) were searched as well as hand search of references from major publications. Keywords included: genetic screening, genetic testing, psychological, psychological well-being, psychological adjustment, stress, adaptation, cancer worry, disease worry, and distress. Selection criteria for the literature review included studies with a follow-up design or review articles. Each selected study was reviewed by two reviewers on its quality of evidence and generalizability using a standardized template. A total of 73 relevant studies were identified among the disease groups: 49 on cancer, 20 on HD, 2 on Hemochromatosis, and 2 described mixed conditions.

Risk factors for psychological distress identified by the literature review provided the basis for item generation. Items were written in a mixed format where respondents were asked for their endorsement of each statement ranging from Yes/No for risk factors of binary nature, to a 5-point likert-type scale for risk factors with stages in frequency and/or intensity. The instrument items were further refined by 10 genetic service providers (3 geneticists, 4 genetic counselors, 2 oncologists, 1 genetics nurse) rating items on *comprehension, readability, and perceived clinical relevance* using a ten-point scale with 0 being "excellent/definitely relevant" and 10 being "very poor/definitely not relevant". Risk factor items were removed if rated above five by more than 3 providers. Providers were also asked to suggest additional risk factor items. These suggestions were checked against the literature for empirical evidence. Following this step, 7 volunteers undergoing genetic testing for AOHDs were recruited to try out the scale for clarity, succinctness and relevance from the clients' perspectives. At this stage, the proposed instrument consisted of 56 items: demographics (4 items); perceived risk (8 items); life events and family history of the disease (8 items); perceived impact of carrying a mutation (9 items);

family communication (6 items); disease specific concerns (5 items); optimism (3 items); social support (3 items), pre-morbid functioning and previous psychiatric history (10 items).

Item refinement:

Subjects: Following informed consent, a convenient sample of 141 participants who had given blood for genetic tests at the Toronto and Ottawa sites completed the GPRI (using a three patients per item ratio) to select the best items for the candidate scale. The participants were middle aged (48.67 ± 13.29), mostly female (77%) testing for hereditary breast cancer, and many (65%) had already suffered the onset of the illness.

Scoring: To ensure that binary items carry an equal weight as the 5-point likert-type items, a score of 5 was assigned to *Yes* and 1 to *No.* A score of 3 or mean-substitute was assigned to *Not Applicable* to allow it to be counted in the total score. Reliability analysis was carried out and a Cronbach's Alpha was set for .75 or higher for the scale to move to the next phase [26]. Any item with an item-total correlation less than .20 was identified for potential removal. Using team consensus, a total of 19 items were removed, combined or substituted, resulting in a 37 item GPRI candidate scale at the end of phase I.

Phase II: Scale Validation

Subjects: Individuals undergoing genetic testing for one of the AOHDs in each of the five study sites were invited to participate: 1) age 18 or above undergoing genetic testing for cancer, HD, or Hemochromatosis; 2) fluent in English; and 3) residing within 1.5 hours driving distance from study site. Although the onset of an AOHD was not an exclusion criterion, individuals in advanced stages of the illness and / or who were unable to consent due to cognitive impairment

were excluded. At baseline, participants were asked to complete a set of self-report questionnaires (e.g. Brief Symptom Inventory, etc.) described below within a one month period following the provision of a blood sample. For those who received a genetic test result, questionnaires were mailed within two weeks to one month of the disclosure of test result. These participants were also telephoned to complete the Hamilton Depression and Hamilton telephone-based Anxiety Scales to further assess depressive and anxiety symptoms. .

Materials**:** At baseline, three psychosocial measures were used: *GPRI Candidate Scale* from Phase I. To facilitate scoring of the scale by genetic providers, scores for response to each item on the GPRI were imbedded in the questionnaire, where clinicians could calculate a total score in less than 5 minutes. *Brief Symptom Inventory* (BSI) The BSI is a 53-item measure of psychological distress that contains three global scales i) depression, ii) anxiety and iii) somatization [27]. While it has some limitations being a self-report measure it has been well-validated and widely used in medical and psychiatric populations to assess psychological functioning; *Impact of Event Scale (IES)*: The IES is a 15-item, likert-style scale used to assess the experience of a specific stress response and is designed to be easily anchored in relation to a specific stressor or life event. It has been extensively utilized in the genetics literature to assess genetic testing-related distress; we similarly anchored the IES items in relation to the anticipation of the genetic test result at baseline and in relation to the actual genetic test at follow- up . The IES has two sub-scales: i) intrusive thoughts and feelings associated with the stressful life event, and ii) items associated with patterns of avoidance of certain thoughts, feelings, or situations [28].

Measures at one month post genetic testing results included: the self -reports scales of the BSI, IES and each participant received a telephone call for the telephone-based Hamilton

Depression 29-item Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A). The HAM-D evaluates depressed mood, vegetative and cognitive symptoms of depression, and comorbid anxiety symptoms [29]. The HAM-A quantifies the severity of anxiety symptomatology and consists of 14 items. The HAM-D and HAM-A have demonstrated validity in clinical interview, in person or by telephone [30]. These two instruments were selected as main outcome measures based on the literature that the standardized interview based-rating scales should be used over subjective report scales as the principal outcome criterion in psychological distress both in general practice and in research trials [34]. Cases would be defined by established cut-offs from the literature for HAM-D >=12 [35] or HAM-A >=10 [36]. These cut off points were established for populations in general practice, which was our study population.

The one-month follow-up time point was selected as it is when elevated distress might occur [31]. In addition, the 2-week duration criterion for depression defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) is met by this time frame.

Assessing Psychometric Property of the Scale

As a first step, items were required to have at least an 80% response rate. Second, each item was examined to determine its contribution to the internal consistency of the total 37-item scale. The minimum item-total correlation was set at .20 [32].

A principal components factor analysis with varimax rotation was performed on the candidate scale to examine the factor structure and the loading of the items. To assess the *convergent validity* of the candidate scale, the correlations between baseline GPRI, IES and BSI were calculated. To assess the *sensitivity, specificity and predictive value* of the GPRI, the

follow-up HAM-D and HAM-A were used to identify "cases" who met cut offs for either the depression or anxiety symptomatology. For example, participants with a high GPRI at baseline would be classified as "at risk" for future onset of adjustment difficulties. This would be confirmed by a high HAM-D or HAM-A score or "case" during 1 month follow-up. Similarly, those with a low GPRI score should receive low score in HAM-D or HAM-A as "non-cases". The predictive value of the GRPI, describing the number of test-positives (in our case, high GPRI) who truly have the psychological condition (i.e. cases identified by HAM-D or HAM-A), was tested by a Receiver Operating Characteristic (ROC) curve which visually plotted the true positive rate (sensitivity) over false positive rate (1-specificity). We included cases to be identified by either anxiety and/or depressive symptomatology as both have been reported in the literature [8, 9].

To address the issue of missing follow-up data in a cohort study, as suggested in the literature [33], we tested the assumption that the sub sample with missing data had a similar baseline exposure (similar GPRI) as the non-missing subsample by comparing baseline GPRI between the participants and dropouts. This step assesses if there was systematic bias resulting from the loss of information in the follow-up period.

RESULTS

Participant characteristics

Study packages were mailed to 1129 individuals interested in hearing more about the study. Of these individuals, 722 of them consented and 712 (98%) completed the GPRI. Most participants were tested for the inheritable cancers, while a small percentage of participants were tested for

hemochromatosis and HD. Similar to phase I, phase II participants were mostly female, at mid-life stage, and more than half had a past diagnosis of the disease (see table 1).

Insert Table 1 about Here

Of the 712 participants, 85 (12%) did not receive genetic testing results at the scheduled follow-up time and were not eligible for follow-up measures on psychological symptoms in response to a genetic testing result. Of the remaining 627 participants, 152 (24%) did not return the self-administered follow-up questionnaires and 12 (2%) submitted the follow-up questionnaire package but did not complete a standardized telephone interview using HAM-D and HAM-A (up to 4 telephone calls were made to reach each participant). Therefore the final number of participants with complete follow-up data is 463 (74%). The age, and baseline GPRI score between individuals who did not receive genetic testing results (age 51.4±12.7, GPRI 49.3±12.7), those who did not return the follow-up questionnaires (age 48.1±11.6, GPRI 50.2±14.4) and those who completed follow-up measures (age 50.1±12.8, GPRI 49.1±13.5) were compared. There was no statistically significant group difference (ANOVA and all post-hoc comparisons $p>0.05$).

Because of the similarity between the dropouts and completers, we proceeded with reliability and validity analysis of the tool using the subsample that provided outcome data.

We carried out the calculations for distress level, for example, for depression and anxiety symptoms using the BSI data, for specific distress associated a genetic test result using the IES. Approximately, 13.0% to 20.1% of participants reached the threshold of moderate to severe distress respectively (see table 2).

Insert Table 2 about Here

HAM-D and HAM-A interview data from 463 participants were used as a further validation tool to measure psychological symptoms post genetic testing results. Defined by cut-offs for HAM-D >=12 [35] or HAM-A >=10 in the literature [36], the rates for psychological distress of either depression or anxiety was 13.7% (N=63). The rate was 13% for HD, 15% for breast cancer and 7% for Lynch Syndrome.

Reliability and Factor Analysis

A reliability analysis was performed on 37 items. Twenty items belonging to 18 questions were selected based on the criteria for item selection described in the methods section. The Cronbach's alpha of the 20 item GPRI was 0.81 suggesting a good level of internal consistency.

The factor analysis resulted in a psychometrically sound 3-factor solution, with subscales representing the dimensions of: 1) *Perceived impact and personal adjustment to genetic testing* (12 items); 2) *Past history of mental health concerns* (5 items) and 3) *Personal history/family history/loss to cancer* (3 items). All three factors met the minimum Eigenvalue criteria of 1.

The first, 12-item factor (ALPHA = 0.85), accounting for 22% of the variance, includes items associated with the anticipated or experienced impact of being at high risk for AOHD. Example items included: "My worries about the disease affect my daily mood"; "The disease for which I am at risk is currently causing a significant disruption in my family life".

The second 5-item factor (ALPHA = 0.76), accounted for an additional 14% of the total variance, and reflected a sense of a person's past history or vulnerability in the area of mental health , e.g. "I have had emotional problems in the past", These items have been used in other medical health areas [37, 38] and tend to be predictive of maladjustment [20] following a life event.

The third 3 item factor (ALPHA = 0.08), accounted for 8% of the total variance and pertained to personal or family-related experiences associated with the hereditable disorder for which the participant is undergoing testing. . Examples include: "I have a personal diagnosis of the disease for which I am receiving counseling"; "I lost a close family member to the disease for which I am receiving counseling"; and "I have taken care of a very ill parent or another close family member". These 3 final items had low item total correlation because they were different from the rest of the items in that they focused on direct experiences related to the illness, rather than psychosocial-related items. These items were kept in the scale as they contributed significantly to the overall variance, and correlated highly with HAM-D and HAM-A. To determine the relationships between the three factors/subscales, correlations were computed. Factor1 and factor2 had moderate correlations with each other (factor1/factor2 $r=0.30$, $p<0.01$). The correlation of the first two factors with factor3 was much lower as expected (factor1/factor3 $r=0.06$, and factor2/factor3 $r=0.01$, not statistically significant). These results support the multidimensional character of the GPRI scale (see Table 3).

Insert Table 3 about Here

One additional statement "I am interested in talking to a counselor about one or more of these concerns" was added to the tool at the end as suggested by participants and providers to remind them the option of seeing a counselor if required. This statement is not part of the items examined during the instrument development and therefore does not carry a score.

The total score for the 20 item GPRI ranged from 20 to 100, with a sample mean 49.36 ± 13.23. The total was calculated by the sum of the raw scores for each of the statements. Females had a significantly higher score for the GPRI than males (50.37 ± 13.14 vs. 41.91 ± 11.47,

p<0.01), and participants testing for HD had a higher, but non-significant score than participants testing for cancer (52.24±13.24 vs. 49.37±13.22, n.s.).

Validity

Construct validity – correlations: The GPRI was assessed for its correlation with other standardized self-report measures of psychological functioning collected at baseline. Convergent validity was demonstrated by the correlation between the GPRI and the following measures: a positive correlation with the IES total score at r = .51, p< .001, and with BSI at r = .58, p< .001.

Sensitivity, specificity and the predictive value of GPRI for future distress: The telephone interview-based HAM-D and HAM-A were used to identify subjects who presented specific psychological symptoms of distress such as depression and/or anxiety during the one month post genetic testing follow-up. A total of 63 "cases" (13.6% of 463 completers) were identified as having psychological distress levels above specified thresholds defined in the methods section for either anxiety or depression symptoms or both. About 23% among participants testing positive met the distress threshold, as did 10% among those with negative results, and 20% among uninformative. Participants scoring above HAM-D (N=55) threshold had significantly higher GPRI scores than participants below the threshold (N=408) (61.12±13.27 vs. 47.91±12.27, p<0.01). Same patterns were observed for HAM-A high (N=40) vs. low (N=423) (62.53±12.92 vs. 48.25± 12.43, p<0.01).

Other demographic characteristics of these 63 subjects include: most were female and undergoing testing for BRCA1/2, which was similar to the whole sample of 712 (table 1). Compared with the whole sample, these subjects had a slightly higher percentage of personal history of cancer (65% vs. 62%), higher rate of recent significant event of loss (56% vs. 47%), greater percentage reporting disease worries affecting mood (54.8% vs. 27%), having a feeling of

sadness in the past month (46% vs. 17%) and anxiousness in the past month (33% vs. 17%). Our instrument captured all of these characteristics of this subsample.

The predictive value of a test describes how many of the test-positives (in this case, a high score on GPRI) truly have the psychological condition. An ROC curve was used to plot the true positive rate (sensitivity) over the false positive rate (1-specificity). A good ROC curve rises sharply, indicating a high proportion in true positive and a low proportion of false positives. The ROC curve for the GPRI was 0.78, which is considered as an indicator of an adequate screening instrument [39].

An important purpose of the GRPI in our study was to identify individuals at risk for post genetic testing psychological distress. Therefore, the cutoff value was set to maximize sensitivity – in another word, not to miss detecting a "case". Using a GPRI cut off score of 50, the instrument was able to predict 84% of the "cases" identified by HAM-D or HAM-A conducted post genetic testing results, with a specificity value of 60% (Figure 1).

Insert Figure 1 about Here

DISCUSSION

The aim of this study was to develop a brief, easy-to-use psychosocial screening instrument specific for the genetic testing context and to examine its reliability and validity (Appendix A). To our knowledge this is the first report of a psychosocial screening instrument for use across AOHD. Unlike current psychological instruments used mainly in research studies in genetics clinics to identify existing global symptoms of depression and anxiety, or impacts, the GPRI assesses *psychological risk factors*, such as the specific anticipated impacts of a genetic testing result and the perception of the disease. The GPRI demonstrates promising psychometric

properties as a tool designed to assist genetics health care providers determine which of their patients undergoing genetic testing for AOHD is at increased psychological risk and should likely be considered for additional psychosocial support to facilitate adjustment to a test result.

A high reliability was demonstrated by a Cronbach's Alpha at 0.81, moderate to high item-total correlation and inter-item correlation of the whole scale. The construct validity of the scale was supported by high correlations between the GPRI and standardized psychological measures (BSI, IES). The clinical utility and predictive value of the GPRI was supported as well. A GPRI score above the cutoff of 50 at baseline was able to predict 84% of "distress" cases identified by HAM-D or HAM-A, a strong indicator of its potential usefulness in a clinical setting.

A brief self-administered screening tool will be easy and likely highly acceptable for incorporation into genetics clinics. The GPRI can be completed and scored quickly during clinical visits and without additional burden to patients and health providers. In addition, by focusing specifically on known risk factors associated with inheritable illness, the instrument will be perceived as being more clinically relevant and acceptable to patients. Patients with higher GPRI scores can be flagged and either receive telephone follow-up to further assess concerns or potential distress or be invited back for an appointment for further assessment and required psychological treatment.

Alternatively, genetic clinics with available psychosocial personnel could utilize the tool to guide referrals for a formal psychosocial assessment that can further explore and address specific self-reported psychological factors. For example, in the case where an individual is particularly fearful of developing an illness or is concerned about specific impacts, such as expecting relationship or family communications difficulties, information on communication

strategies, personal coaching or family–based interventions could be employed to support the individual. For an individuals who reports a past history of psychological illness, a mental health professional could further assess current psychological functioning and implement specific approaches, and could offer cognitive-behavioral strategies or psychotropic medication to assist in the management of anxiety or depressive symptoms [40]. Several items incorporate variables related to heritable disease experiences and associated perceptions which can be used to guide educational interventions to correct any myths or beliefs.

The scale appeared highly acceptable to patients. A high face validity will contribute to better scale uptake being perceived as "user friendly" and clinically relevant, compared for example, to a standardized psychological instrument on depression, which have demonstrated some barriers to clinic uptake [19]. The GPRI in contrast might be considered as a "communimetric measure", that is, the items themselves are useful for the clinician in communicating concerns about specific areas of functioning directly with the patient [41].

Left untreated, significant levels of psychological symptoms may lead to lower quality of life [40], and lower satisfaction with genetics services [21]. A psychological screening approach allows both for careful monitoring during a known stressful period-that of awaiting test results [42], and provides an opportunity for any planned follow-up care. Flagging those individuals who might benefit most from psychosocial care also best utilizes the often limited psychological resources in genetic clinics [2, 20, 21].

Our study findings are limited by the characteristics of the sample, in that most participants were female and undergoing testing for *BRCA1/2*. This pattern is similar to that observed in the literature on genetic testing for AOHD, which is predominantly focused on Hereditary Breast-Ovarian Cancer Syndrome. We attempted to obtain a larger sample of

individuals undergoing genetic testing for HD or Lynch Syndrome which would presumably provide a greater sample of males. However, these sample pools were much smaller. However, this study and the resulting GPRI represent an attempt to begin the development of a general tool that addresses concerns that are relevant across genetic samples. Our belief stemming from clinical practice and the associated literature suggest that the identified mental health issues or adjustment risk factors are not disease specific. We suggest that future studies further address the validity of GPRI in male populations and in the rare adult onset hereditary diseases, such as HD. Future studies should also include randomized controlled trials to assess the effectiveness of the GPRI in predicting distress, its impact on referral patterns, patient and provider satisfaction, as well as on cost-effectiveness. The GPRI could also be evaluated in primary care settings where genetics services might be offered more frequently to meet the demand.

CONCLUSIONS

This is the first study to develop a screening tool specifically to help identify individuals undergoing genetic testing for AOHD who are at increased psychological risk. The study resulted in an easy to use, 20-item scale consisting of 3 factors with promising psychometric properties. The GPRI has the potential to be used as a clinical screening tool and as a validated measure for future studies. Future work can examine its impact on clinical referral patterns within the field of genetics, and on its acceptability, reliability and validity with larger samples of individuals undergoing genetic testing for HD, Lynch Syndrome, and potentially for emerging new genetic tests, such as for cardiac or psychiatric disorders.

Acknowledgement

The first author is a recipient of a career scientist award from the Canadian Institutes of Health Research (CIHR) and the Ontario Women's Health Council. This study was funded by Canadian Institutes of Health Research (CIHR) Grant No. AHC 73144. We would like to express our gratitude to all the genetic testing patients who participated in our study. Thank you for your contribution towards this very important work and the development of the instrument. Thank you also to the genetic counselors and clinic staff from the participating genetic centers who assisted in recruitment: Children's Hospital of Eastern Ontario (Eastern Ontario Regional Genetics Centre); North York General Hospital (Clinical Genetics); Mount Sinai Hospital (Familial GI Cancer Registry & Familial Breast Cancer Clinic); Princess Margaret Hospital (Familial Breast & Ovarian Cancer Clinic); and BC Cancer Agency (Hereditary Cancer Program). We would also like to thank the research staff for their commitment and hard work to complete this national multi-site study. Finally, the team would like to pay special recognition to the late Dr. Anne Summers, who was co-investigator on the team. Her dedication to the need for empirically based tools and her strong vision to support recipients of new genetic technology were key influences in the conceptualization, funding and completion of this study.

Ethics: Research Ethics Board approval was obtained at all five participating sites: Toronto (Mount Sinai Hospital, North York General Hospital, Princess Margaret Hospital); Ottawa (Children's Hospital of Eastern Ontario); and Vancouver (British Columbia Cancer Agency).

Data Sharing Statement: There is no additional data available

Conflict of Interest: The authors do not have any conflict of interest to disclose.

Funding: This study was funded by Canadian Institutes of Health Research (CIHR) Grant No. AHC 73144.

Contributorship Statements

Dr. Mary Jane Esplen

Principal Applicant responsible for leading all aspects of the research, oversees budget, hiring staff, supervising data collection, analysis and interpretation, and writing of all manuscripts and reports.

Dr. Mario Cappelli

Co-principal inv. responsible for assisting in item generation and refinement, the implementation of data collection, interpretation of findings and writing of manuscripts and reports.

Dr. Jiahui Wong

Co- Applicant responsible assisting in instrument development, statistical procedures, sampling and interpretation of findings and writing of manuscripts and reports.

Dr. Joan Bottorff

Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services, development of guidelines and writing of manuscripts and reports.

Dr. Jon Hunter

Co-Applicant responsible for assisting in item generation and refinement, guideline development, interpretation of findings and writing of manuscripts and reports.

Dr. June Carroll

Co-Applicant responsible for assisting in item generation and refinement, implementation of the screening validation strategy and development of guidelines, interpretation of findings and writing of manuscripts and reports.

Dr. Michel Dorval

Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services, interpretation of findings and writing of manuscripts and reports.

Dr. Brenda Wilson

Co-Applicant responsible for co-leading the implementation of the consensus guidelines components of the proposed study. Will assist in item generation for tool, interpretation of findings, writing of manuscripts and reports.

Dr. Judith Allanson

Co-Applicant responsible for refining of items, guiding the recruitment of providers/patients and testing of the instrument in genetic services, development of guidelines and writing of manuscripts and reports.

Ms. Kara Semotiuk

Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services and development of guidelines, and writing of manuscripts and reports.

Ms. Melyssa Aronson

Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services, development of guidelines and writing of manuscripts and reports.

Dr. Louise Bordeleau

Co-Applicant responsible for overseeing recruitment at MSH and UHN site in Toronto, testing of instrument and interpretation of findings, writing of manuscripts and reports.

Ms. Nicole Charlemagne

Project coordinator, responsible for: patient recruitment and follow-up; assisting in item generation, refinement, and overall layout and design of tool; data collection, data entry, and data clean-up; revisions and submission of manuscript.

Dr. Wendy Meschino

Co-Applicant responsible for refining of items, guiding the recruitment of providers and testing of the instrument in genetic services, interpretation of findings and writing of manuscripts and reports.

REFERENCES

1. Lerman C, Croyle RT. Emotional and behavioral responses to genetic testing for susceptibility to cancer. *Oncology (Williston Park)*. 1996;**10**:191-5, 9; discussion 200-2.

2. Bleiker EM, Hahn DE, Aaronson NK. Psychosocial issues in cancer genetics--current status and future directions. *Acta Oncol*. 2003;**42**:276-86.

3. Wellisch DK, Lindberg NM. A psychological profile of depressed and nondepressed women at high risk for breast cancer. *Psychosomatics*. 2001;**42**:330-6.

4. Broadstock M, Michie S, Marteau T. Psychological consequences of predictive genetic testing: a systematic review. *Eur J Hum Genet*. 2000;**8**:731-8.

5. Ho SM, Ho JW, Bonanno GA, et al. Hopefulness predicts resilience after hereditary colorectal cancer genetic testing: a prospective outcome trajectories study. *BMC Cancer*. 2010;**10**:279.

6. Trask PC, Paterson AG, Wang C, et al. Cancer-specific worry interference in women attending a breast and ovarian cancer risk evaluation program: impact on emotional distress and health functioning. *Psychooncology*. 2001;**10**:349-60.

7. Coyne JC, Kruus L, Racioppo M, et al. What do ratings of cancer-specific distress mean among women at high risk of breast and ovarian cancer? *Am J Med Genet A*. 2003;**116A**:222-8.

8. Marteau TM, Croyle RT. The new genetics. Psychological responses to genetic testing. *BMJ*. 1998;**316**:693-6.

9. Meiser B. Psychological impact of genetic testing for cancer susceptibility: an update of the literature. *Psychooncology*. 2005;**14**:1060-74.

10. Hamilton JG, Lobel M, Moyer A. Emotional distress following genetic testing for hereditary breast and ovarian cancer: a meta-analytic review. *Health Psychol*. 2009;**28**:510-8.

11. Shaw C, Abrams K, Marteau TM. Psychological impact of predicting individuals' risks of illness: a systematic review. *Soc Sci Med*. 1999;**49**:1571-98.

12. Dorval M, Gauthier G, Maunsell E, et al. No evidence of false reassurance among women with an inconclusive BRCA1/2 genetic test result. *Cancer Epidemiol Biomarkers Prev*. 2005;**14**:2862-7.

13. Cameron LD, Sherman KA, Marteau TM, et al. Impact of genetic risk information and type of disease on perceived risk, anticipated affect, and expected consequences of genetic tests. *Health Psychol*. 2009;**28**:307-16.

14. Smith KR, West JA, Croyle RT, et al. Familial context of genetic testing for cancer susceptibility: moderating effect of siblings' test results on psychological distress one to two weeks after BRCA1 mutation testing. *Cancer Epidemiol Biomarkers Prev*. 1999;**8**:385-92.

15. Dougall AL, Smith AW, Somers TJ, et al. Coping with genetic testing for breast cancer susceptibility. *Psychosom Med*. 2009;**71**:98-105.

16. Esplen MJ, Urquhart C, Butler K, et al. The experience of loss and anticipation of distress in colorectal cancer patients undergoing genetic testing. *J Psychosom Res*. 2003;**55**:427-35.

17. Zabora JR. Screening procedures for psychological distress. In: Holland JC, editor. Psycho-Oncology. New York: Oxford University Press; 1998. p. 653-62.

18. Watson M, Lloyd S, Davidson J, et al. The impact of genetic counselling on risk perception and mental health in women with a family history of breast cancer. *Br J Cancer*. 1999;**79**:868-74.

19. Cella D, Hughes C, Peterman A, et al. A brief assessment of concerns associated with genetic testing for cancer: the Multidimensional Impact of Cancer Risk Assessment (MICRA) questionnaire. *Health Psychol*. 2002;**21**:564-72.

20. Zabora J, BrintzenhofeSzoc K, Curbow B, et al. The prevalence of psychological distress by cancer site. *Psychooncology*. 2001;**10**:19-28.

21. Thewes B, Meiser B, Tucker K, et al. Screening for psychological distress and vulnerability factors in women at increased risk for breast cancer: A review of the literature. *Psychology, Health & Medicine*. 2003;**8**:289-303.

22. Howell D, Keller-Olaman S, Oliver T, et al. A Pan-Canadian Practice Guideline: Screening, Assessment and Care of Psychosocial Distress (Depression, Anxiety) in Adults with

Cancer. Toronto: Canadian Partnership Against Cancer (Cancer Journey Action Group) and the Canadian Association of Psychosocial Oncology2010.

23. Read CY, Perry DJ, Duffy ME. Design and psychometric evaluation of the Psychological Adaptation to Genetic Information Scale. *J Nurs Scholarsh*. 2005;**37**:203-8.

24. Jackson D. A sequential system for personality scale development. In: Spielberger C, editor. Current Topics in Clinical and Community Psychology. New York: Academic Press; 1970. p. 61-96.

25. Stuckless N, Goranson R. The vengeance scale: Development of a measure of attitudes toward revenge. *Journal of Social Behavior and Personality*. 1992;**7**:25-42.

26. Briggs SR, Cheek JM. The role of factor analysis in the development and evaluation of personality scales. *Journal of Personality*. 1986;**54**:106-48.

27. Derogatis LR. The brief symptom inventory (BSI). Administration, Scoring and Procedures Manual. 3rd ed. New York: National Computer Systems; 1993.

28. Horowitz MJ, Wilner N, Alvarez W. Impact of Events Scale: A Measure of Subjective Stress. *Psychosomatic Medicine*. 1979;**41**:209-18.

29. Hamilton MA. A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*. 1960;**23**:56-23.

30. Katzelnick DJ, Simon GE, Pearson SD, et al. Randomized trial of a depression management program in high utilizers of medical care. *Arch Fam Med*. 2000;**9**:345-51.

31. DudokdeWit AC, Tibben A, Duivenvoorden HJ, et al. Predicting adaptation to presymptomatic DNA testing for late onset disorders: who will experience distress? Rotterdam Leiden Genetics Workgroup. *J Med Genet*. 1998;**35**:745-54.

32. Walsh W, Betz N. Tests and Assessments. New Jersey: Prentice Hall Inc; 1985.

33. Melnick EL, Everitt BS. Quantitative risk analysis and assessment. Hebokea NJ: John Wiley & Sons; 2008.

34. Moller HJ. Rating depressed patients: observer- vs self-assessment. *Eur Psychiatry*. 2000;**15**:160-72.

35. Aben I, Verhey F, Lousberg R, et al. Validity of the beck depression inventory, hospital anxiety and depression scale, SCL-90, and hamilton depression rating scale as screening instruments for depression in stroke patients. *Psychosomatics*. 2002;**43**:386-93.

36. Pasquini M, Biondi M, Costantini A, et al. Detection and treatment of depressive and anxiety disorders among cancer patients: feasibility and preliminary findings from a liaison service in an oncology division. *Depress Anxiety*. 2006;**23**:441-8.

37. Beck CT. A checklist to identify women at risk for developing postpartum depression. *J Obstet Gynecol Neonatal Nurs*. 1998;**27**:39-46.

38. Reid AJ, Biringer A, Carroll JD, et al. Using the ALPHA form in practice to assess antenatal psychosocial health. Antenatal Psychosocial Health Assessment. *CMAJ*. 1998;**159**:677-84.

39. Goutham R. What is an ROC curve? *The Journal of Family Practice*. 2003;**52**:695.

40. Esplen MJ, Hunter J. Therapy in the Setting of Genetic Predisposition to Cancer' in 'Handbook of Psychotherapy in Cancer Care. In: Watson M, Kissane D, editors. Handbook of Psychotherapy in Cancer Care. London: John Wiley & Sons Ltd; 2011. p. 201-12.

41. Lyons JS. A Communication Theory of Measurement in Human Service Settings. New York: Springer; 2009.

42. Broadstock M, Michie S, Gray J, et al. The psychological consequences of offering mutation searching in the family for those at risk of hereditary breast and ovarian cancer--a pilot study. *Psychooncology*. 2000;**9**:537-48.

Table 1
Description of Phase II Participants Characteristics (N=712)

Variables in GPRI*		
Age in years: mean (SD)		49.80 (+12.53), range 18-80, median 50.00
Gender: n (%)	Male Female	85 (12%) 627 (88%)
Type of AOHD being tested: n (%)	Cancer (BRCA) Cancer (other, ie, Colon) Huntington disease Hemochromatosis	580 (82%) 90 (13%) 31 (4%) 5 (1%)
Personal history of disease being tested: n (%)		441 (62%)
Recent significant event (diagnosis of or loss of significant others to the disease being tested): n (%)		333 (47%)
Disease worries affect daily mood (strongly agree or somewhat agree): n (%)		189 (27%)
Sad in the past month (often or almost all the time): n (%)		121 (17%)
Anxious in the past month (often or almost all the time) n (%)		121 (17%)

* Note: there are missing data for some GRPI variables. The total count for each variable do not necessarily add up to 712

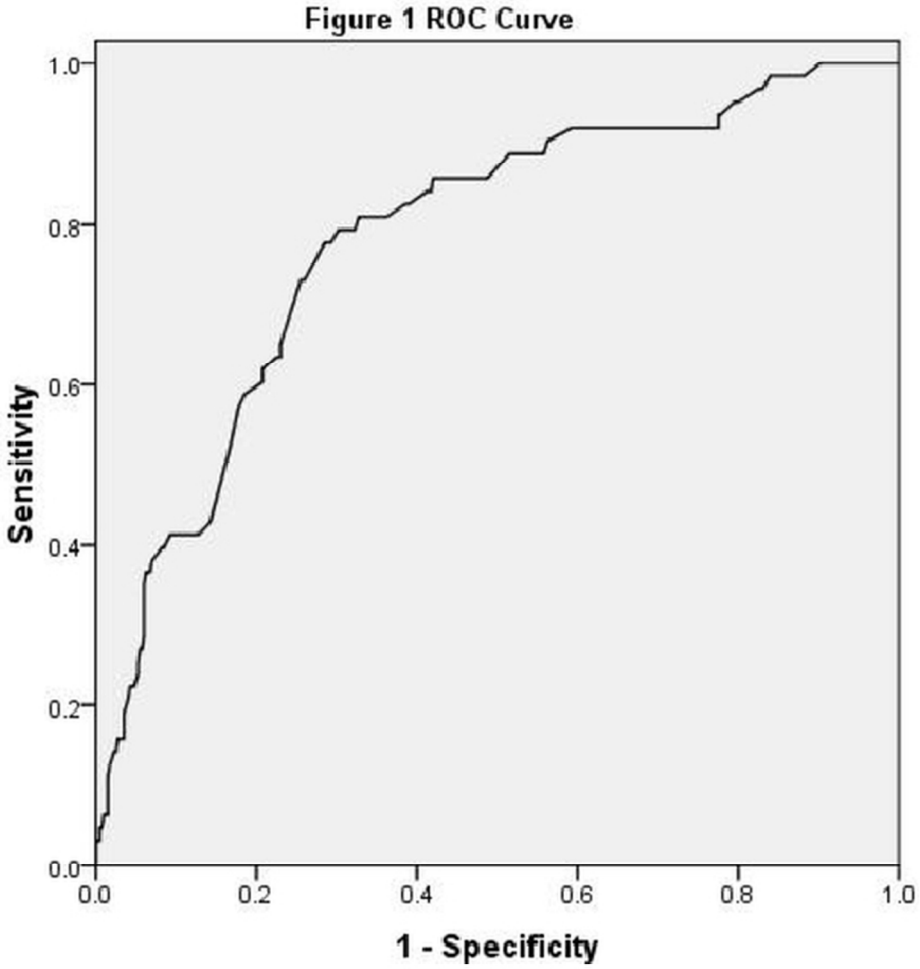
Table 2
Psychological Symptom of Distress 1 Month Post Genetic Testing Results By Disease Type (N=475)

	Overall N (%)	Huntington	*BRCA*	Other Cancer
IES intrusion >=17[a]	60 (13.0%)	5 (23.8%)	51 (12.5%)	4 (9.5%)
IES avoidance >=17[a]	65 (13.7%)	5 (23.8%)	57 (14.0%)	3 (7.1%)
BSI-18 total >=13[b]	95 (20.1%)	6 (28.6%)	86 (21.1%)	3 (7.1%)

a. Shemesh E. et al (2004) Posttraumatic stress, non adherence, and adverse outcome in survivors of a myocardial infarction. Psychosomatic Medicine, 66: 521-526
b. Zabora et al (2001): A new psychosocial screening instrument for use with cancer patients. Psychosomatics, 42:241–246

Table 3
GPRI Factor Solutions and Factor Loadings

	Factor Loadings	Commu-nalities	Item-Total	Item Mean
• My worries about the disease affect my daily mood	.759	.652	.582	2.22
• I worry often about my risk of getting the disease	.742	.551	.529	2.67
• I am concerned about my risk of getting the disease	.656	.484	.472	3.28
• I have generally felt nervous and anxious in the past month	.652	.538	.600	2.54
• I have generally felt sad in the past month	.627	.524	.572	2.58
• If I learn that I have a genetic mutation, … I will have more problems in my life	.617	.406	.399	2.79
…I will have difficulties with my family relationships	.513	.324	.424	1.62
… I will change plans for my career	.451	.228	.262	2.08
• The disease is currently causing a significant disruption in my family life	.568	.408	.463	2.42
• I am worried that my test result will impact on my relationship with my significant other	.546	.308	.383	2.54
• I am worried about talking to my children about the heritable nature of the disease for which I am being tested	.522	.326	.453	2.04
• I feel guilty that I might pass on the disease risk to my children	.508	.276	.414	3.11
Factor 1: Anticipated or experienced impact of having a disease risk or genetic mutation: 12 statements, Cronbach's alpha = .85, inter – item correlation = .32, variance explained = 22%				
• I have had emotional problems in the past	.796	.655	.423	2.66
• I have been diagnosed with a depressive or anxiety disorder in the past	.769	.596	.349	2.01
• I have had counselling with a mental health professional in the past	.762	.593	.433	2.85
• I have had emotional problems that led me to thoughts about suicide	.623	.389	.262	1.45
• I am now seeing a counselor for one or more of these emotional concerns	.509	.272	.274	1.35
Factor 2: Personal history or vulnerability to mental health issues or symptoms: 5 items, Cronbach's alpha = .76, inter – item correlation = .39, variance explained = 14%				
• I have taken care of a very ill parent or another close family member	.687	.493	.116	2.36
• I lost a close family member (e.g. parent/ sibling) to the disease for which I am receiving counseling/testing	.667	.445	-.002	2.87
• I have/had a personal diagnosis of the disease for which I am receiving counseling/testing	-.642	.413	-.073	3.47
Factor 3: Personal or family history of the genetic disease being tested in the clinic: 3 items, Cronbach's alpha = .08, inter – item correlation = .03, variance explained = 8%				



90x98mm (300 x 300 DPI)

Appendix A Genetic Psychosocial Risk Instrument (GPRI)

The purpose of this questionnaire is to help identify individuals who may need additional support while going through genetic testing. The questions are about your life experiences and feelings about the disease for which you are receiving genetic testing/counseling. Please note that whenever the word "disease" is used, it is referring to the disease for which you are having genetic testing and/or counseling. Please read each statement carefully, then respond by placing a firm checkmark in the most appropriate space.

Name:	Date (dd / mm / yyyy):

1. I have/had a personal diagnosis of the disease for which I am receiving counseling/testing (5) Yes (1) No
2. I have taken care of a very ill parent or another close family member (e.g. sibling) (0) Yes (1) No
   If yes, the illness was related to the condition for which I am receiving counseling/testing (5) Yes (3) No
3. I lost a close family member (e.g. parent/sibling) to the disease for which I am receiving counseling/testing (5) Yes (1) No
   If yes, please indicate who the family member was who died (check all that apply):
   (0) a parent (0) a sibling (0) other (specify)_____

	Strongly agree	Somewhat agree	Neither agree/disagree	Somewhat disagree	Strongly disagree	Not applicable
4. If I learn that I have a genetic mutation, I believe that:						
a. I will have more problems in my life	5	4	3	2	1	0
b. I will change plans for my career/ profession	5	4	3	2	1	3
c. I will have difficulties in my family relationships	5	4	3	2	1	3
5. The disease for which I am at risk is currently causing a significant disruption in my family life	5	4	3	2	1	3
6. I am worried that my test result will impact on my relationship with my significant other (or future partner)	5	4	3	2	1	3
7. I am worried about talking to my children (young or adult) about the heritable nature of the disease for which I'm being tested	5	4	3	2	1	3
8. My worries about the disease affect my daily mood	5	4	3	2	1	3
9. I worry often about my risk of getting the disease	5	4	3	2	1	3
10. I am concerned about my risk of getting the disease	5	4	3	2	1	3
11. I feel guilty that I might pass on the disease risk to my children	5	4	3	2	1	3

	Almost all of the time	Often	Sometimes	Hardly ever	Not at all
12. I have generally felt sad in the past month	5	4	3	2	1
13. I have generally felt nervous and anxious in the past month	5	4	3	2	1

14. I have had emotional problems in the past (5) Yes (1) No
15. I have had counseling with a counselor and/or a mental health professional in the past (5) Yes (1) No
16. I have been diagnosed with a depressive or anxiety disorder in the past (5) Yes (1) No
17. I have had emotional problems that led me to have thoughts about suicide (5) Yes (1) No
18. I am now seeing a counselor for one or more of these emotional concerns (5) Yes (1) No

19. I am interested in talking with a counsellor about one or more of these concerns (0) Yes (0) No

Instruction to the user: Item #19 is for referral purpose only, no score is assigned. The remaining items all have assigned scores. Because item #4 has three sub-statements, a total of 20 statements/items are included in the scoring.
Please sum the score of all items & enter the total score here _____. If it is 50 or greater, and if #19 is Yes, then a psychosocial referral is recommended.