



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

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Title

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

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

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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].

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3 The risk factors for psychological distress amongst individuals undergoing genetic testing
4 have been delineated in several studies [4, 8, 9]. While there is generally elevated distress
5 among those who receive positive test results [9-11], individuals testing negative or receiving
6 uninformative results may also have adjustment difficulties [12]. For example, individuals may
7 feel guilt or continue to worry about their disease risk [2, 7, 12]. These findings highlight the
8 importance of considering risk factors in addition to the test result itself. Individuals who have
9 elevated distress at the pre test stage and those with a previous psychiatric history (i.e.,
10 depression) are particularly at risk for an adverse psychological outcome after testing [2, 8, 9].
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15 Additional risk factors for distress are more specific to the genetics context and include
16 the level of penetrance of the gene mutation or degree of certainty of developing the disease [4].
17 The perception of control over the disease (including the number of prevention/treatment
18 options) and perception of the immediacy of risk (proximity in age to perceived disease onset)
19 are important predictors [4, 13]. The expectation of a negative test result can play a role in
20 adjustment, as can the context of test results of other family members [9, 14]. As in other
21 medical areas, specific coping styles can affect adjustment [15]. The prior experiences with loss
22 of family members to disease, as well as the developmental level (i.e. young age) of the
23 individual at the time of the loss [2, 3, 16] are significant factors affecting potential adjustment.
24 In addition, the prior experience of giving care to a family member with the disease and lower
25 levels of social support have been associated with poorer adjustment following a positive test
26 result [2-4, 8, 16].
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50 It is clear that there is not one predominant factor, but rather, a series of variables that
51 may contribute to elevated levels of psychological distress [2, 17]. Emotional reactions may
52 impede the assimilation of risk information and the adoption of preventive measures [2, 18].
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3 Psychological distress occurs along a continuum [19, 20] and can be difficult to identify by
4 health professionals [21]. Distress may not become manifest to the health care team until the
5 patient reaches an observable crisis level, i.e. the onset of severe depression or anxiety, or
6 significant conflicts with the family. An early screening instrument would enable healthcare
7 providers to identify patients being at higher psychological risk in order that appropriate support
8 can be given at the right time. In fact, there is now a general consensus that genetic testing
9 should be accompanied by psychological support to promote optimal adjustment [2, 22].
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22 **Screening for Psychological Risk Factors- Why is it necessary?**

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24 The gold standard for identifying psychologically distressed individuals involves structured
25 clinical interviews administered by a clinical psychologist or psychiatrist [21]. However, it is too
26 costly and often not feasible in genetic clinics. Standardized measures of psychological
27 functioning can also be used as a method for identifying distress. However, few clinics use these
28 measures in practice because of personnel and time requirements for scoring and interpretation
29 of them. Furthermore, these instruments tend to identify global symptoms that are consistent
30 with the diagnostic classifications of anxiety and/or depression and may lack sensitivity to the
31 important and unique issues that surround genetic testing; issues that may include concerns about
32 family members, past experiences with an inheritable disease, and uncertainty about risk
33 reduction options [19, 21]. In addition, items on these measures typically focus on symptoms of
34 anxiety or depression, rather on variables associated with heritable disease or genetic testing or
35 risk, which may pose barriers for use by genetics health service providers who may prefer
36 instruments that at face value, appear to them and their patients as being more relevant to the
37 genetic testing context.
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3 More recently, new outcome measures designed to assess the psychological impact of
4 receiving genetic information have been developed. For example, the MICRA- is designed to
5 assess concerns and impacts associated with genetic testing for BRCA1/2 [19] and the
6 Psychological Adaptation to Genetic Information Scale is now available [23]. While these
7 measures will require further validation, they provide more clinically relevant approaches to
8 capturing specific impacts of genetic information, such as the sense of increased vulnerability
9 and continued uncertainty often experienced following genetic testing [19, 23].
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20 Measures of global psychological functioning and the evolving outcome measurement
21 tools for the genetics field are not designed to “predict” vulnerability for future distress, but
22 rather, measure current distress levels. Screening, in contrast, is a rapid, cost-effective
23 alternative [21] to prospectively identify individuals who may experience significant difficulty in
24 their attempts to adapt to their genetic information and any associated treatment options [17]. A
25 screening tool enables providers to offer timely and focused educational and psychosocial
26 interventions to prevent future distress.
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36 The primary *objective* of this study was to develop a brief, reliable and valid screening
37 instrument for use in the genetic testing context. The new instrument aimed to incorporate
38 empirically based risk factors for psychological distress and would need to show a high
39 sensitivity, specificity and predictive validity indicating risk for future distress post genetic
40 testing results. A cutoff point would be determined to guide clinical decisions as to whether or
41 not to refer, further assess, or intervene to reduce an individual’s expressed concern.
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51 52 53 **METHODS AND MATERIALS** 54 55 56 57 58 59 60

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3 The study was carried out from September 2005 to July 2010, with research ethics board
4 approval from participating genetics clinics: Toronto (Mount Sinai Hospital, North York General
5 Hospital, Princess Margaret Hospital); Ottawa (Children's Hospital of Eastern Ontario); and
6 Vancouver (British Columbia Cancer Agency). Individuals beginning the genetic testing process
7 for AOHD at each site were approached by genetic counsellors on the project team for their
8 permission to be contacted about the study. Those who expressed interest were mailed the
9 baseline package that included the informed consent. The informed consent included all
10 components of the study, including questionnaires, follow-up phone calls, telephone interviews,
11 as well as to the release of their genetic testing information to the research team.
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24 A two phase approach was used for this study: **Phase I: Item Generation and Refinement**,
25 and **Phase II: Validation**. The multi-stage method [24] takes validation into consideration at
26 each stage of scale development and has been used successfully in previous studies [25].
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34 **Phase I: Item Generation and Refinement.**

35 ***Item generation***

36 To generate items for the Genetic Psychosocial Risk Instrument (GPRI), a literature search was
37 performed for the following AOHDs: Cancer (Hereditary Breast-Ovarian Cancer Syndrome/
38 Lynch Syndrome), Huntington Disease (HD), and Hemochromatosis. These diseases were
39 selected as they represented the majority of patients attending genetic clinics and had an
40 associated available psychosocial literature for review. Databases including Cinahl (1982 to
41 2006), Medline (1966 to 2006), PsychInfo (1985 to 2006), and Pubmed (1985 to 2006) were
42 searched as well as hand search of references from major publications. Keywords included:
43 genetic screening, genetic testing, psychological, psychological well-being, psychological
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3 adjustment, stress, adaptation, cancer worry, disease worry, psych functioning, and distress.
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5 Selection criteria for the literature review included studies with a follow up design or review
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7 articles. Each selected study was reviewed by two reviewers on its quality of evidence and
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9 generalizability using a standardized template. A total of 73 relevant studies were identified
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11 among the disease groups: 49 on cancer, 20 on HD, 2 on Hemochromatosis, and 2 described
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13 mixed conditions.
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17 Risk factors for psychological distress identified by the literature review provided the
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19 basis for item generation. Items were written in a mixed format where respondents were asked
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21 for their endorsement of each statement ranging from Yes/No for risk factors of binary nature, to
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23 a 5 point likert-type scale for risk factors with stages in frequency and/or intensity. The
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25 instrument items were further refined by genetic service providers rating items on
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27 *comprehension, readability, and perceived clinical relevance* using a ten-point scale with 0 being
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29 "excellent/definitely relevant" and 10 being "very poor/definitely not relevant". Risk factor items
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31 were removed if it was rated below five. Providers were also asked to suggest additional risk
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33 factor items. These suggestions were checked against the literature for empirical evidence.
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35 Following this step, 7 volunteers undergoing genetic testing for AOHDs were recruited to try out
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37 the scale for clarity, succinctness and relevance from the clients' perspectives. At this stage, the
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39 proposed instrument consisted of 56 items: demographics (4 items); perceived risk (8 items); life
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41 events and family history of the disease (8 items); perceived impact of carrying a mutation (9
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43 items); family communication (6 items); disease specific concerns (5 items); optimism (3 items);
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45 social support (3 items), pre-morbid functioning and previous psychiatric history (10 items).
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55 ***Item refinement:***
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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.

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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.

34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 **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

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3 genetic test results, participants were mailed the follow-up questionnaires and received a
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5 telephone interview from the project team for the assessment of distress.
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8 Materials: At baseline, three psychosocial measures were used: GPRI Candidate Scale
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10 from Phase I. To facilitate scoring of the scale by genetic providers, scores for response to each
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12 item on the GPRI are imbedded in the questionnaire, where clinicians can calculate a total score
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14 in less than 5 minutes. Brief Symptom Inventory (BSI) The BSI is a 53-item measure of
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16 psychological distress that contains three global scales i) depression, ii) anxiety and iii)
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18 somatization [27]. It is widely used in medical and psychiatric populations to assess
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20 psychological functioning; Impact of Event Scale (IES): The IES is a 15-item, likert-style scale
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22 used to assess the experience of stress and is designed to be easily anchored to have individuals
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24 report on items in relation to a specific stressor or life event (i.e. the stress of a positive genetic
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26 test result). It has two sub-scales: i) intrusive thoughts and feelings associated with the stressful
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28 life event, and ii) items associated with patterns of avoidance of certain thoughts, feelings, or
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30 situations [28].
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36 Measures at one month post genetic testing results included: the BSI, IES and the
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38 telephone based Hamilton Depression 29-item Rating Scale (HAM-D) and Hamilton Anxiety
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40 Rating Scale (HAM-A). The HAM-D evaluates depressed mood, vegetative and cognitive
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42 symptoms of depression, and comorbid anxiety symptoms [29]. The HAM-A quantifies the
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44 severity of anxiety symptomatology and consists of 14 items. The HAM-D and HAM-A have
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46 demonstrated validity in clinical interview, in person or by telephone [30]. The one-month
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48 follow-up time point was selected as it is when elevated distress might occur [31]. In addition,
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50 the 2-week duration criterion for depression defined by the Diagnostic and Statistical Manual of
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52 Mental Disorders, Fourth Edition (DSM-IV) is met by this time frame.
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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

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6 HAM-D and HAM-A interview data from 463 participants were used as a validation tool to
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8 measure distress post genetic testing results. The literature suggests that the observer-rating
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10 scales should be used over subjective report scales as the principal outcome criterion in
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12 psychological distress both in general practice and in research trials [34]. Defined by HAM-D
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14 ≥ 12 [35] or HAM-A ≥ 10 [36], the rates for distress was 13.7%. The rate was 13% for HD,
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16 15% for breast cancer and 7% for Lynch Syndrome.
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22 **Reliability and Factor Analysis**

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24 A reliability analysis was performed on 37 items. Twenty items were selected based on the
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26 criteria for item selection described in the methods section. The Cronbach's alpha of the 20 item
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28 GPRI was 0.81 suggesting a good level of internal consistency.
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32 The factor analysis resulted in a psychometrically sound 3-factor solution, with subscales
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34 representing the dimensions of: 1) Perceived impact and personal adjustment to genetic testing
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36 (10 items); 2) Past history of mental health concerns (5 items) and 3) Personal history/family
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38 history/loss to cancer (3 items). All three factors met the minimum Eigenvalue criteria of 1.
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41 The first, 12-item factor (ALPHA = 0.85), accounting for 22% of the variance, includes
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43 items associated with the anticipated or experienced impact of being at high risk for AOHD.
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45 Example items included: "My worries about the disease affect my daily mood"; "The disease for
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47 which I am at risk is currently causing a significant disruption in my family life".
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50 The second 5-item factor (ALPHA = 0.76), accounted for an additional 14% of the total
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52 variance, and reflected a sense of a person's past history or vulnerability of mental health issues,
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3 e.g. “I have had emotional problems in the past”, These items have been used in other medical
4 health areas [37, 38] and tend to be predictive of maladjustment [20] following a life event.
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8 The third 3 item factor (ALPHA = 0.08), accounted for 8% of the total variance and
9 included a personal or family history of the genetic disease being tested in the clinic. Examples
10 include: “I have a personal diagnosis of the disease for which I am receiving counseling”; “I lost
11 a close family member to the disease for which I am receiving counseling”; and “I have taken
12 care of a very ill parents or another close family member”. These three final items had low item
13 total correlation because they were different from the rest of the items in that they focused on
14 description of personal history, rather than psychosocial-related items. These items were kept in
15 the scale as they contributed significantly to the overall variance, and correlated highly with
16 HAM-D and HAM-A. To determine the relationships between the three factors/subscales,
17 correlations were computed. Factor1 and factor2 had moderate correlations with each other
18 (factor1/factor2 $r=0.30$, $p<0.01$). The correlation of the first two factors with factor3 was much
19 lower as expected (factor1/factor3 $r=0.06$, and factor2/factor3 $r=0.01$, not statistically
20 significant). These results support the multidimensional character of the GPRI scale (see Table
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Insert Table 3 about Here

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

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

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12 Construct validity – correlations: The GPRI was assessed for its correlation with other
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14 standardized measures of psychological functioning at baseline. Convergent validity was
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16 demonstrated by the correlation between the GPRI and the following measures: a positive
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18 correlation with the IES total score at $r = .51$, $p < .001$, and with BSI at $r = .58$, $p < .001$.
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25 Sensitivity, specificity and the predictive value of GPRI for future distress: The HAM-D and
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27 HAM-A were used to identify distress during the one month post genetic testing follow up. A
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29 total of 63 “cases” (13.6% of 463 completers) were identified as having psychological distress
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31 levels above threshold. Of these 63 cases, 55 reported genetic testing results: 18 positive, 26
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33 negative and 11 uninformative. This is equivalent to 23% among participants testing positive,
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35 10% among those with negative results, and 20% among uninformative. Participants scoring
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37 above HAM-D (N=55) threshold had significantly higher GPRI scores than participants below
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39 the threshold (N=408) (61.12 ± 13.27 vs. 47.91 ± 12.27 , $p < 0.01$). Same patterns were observed for
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41 HAM-A high (N=40) vs. low (N=423) (62.53 ± 12.92 vs. 48.25 ± 12.43 , $p < 0.01$).
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47 The predictive value of a test describes how many of the test-positives (in this case, a
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49 high score on GPRI) truly have the psychological condition. An ROC curve was used to plot the
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51 true positive rate (sensitivity) over the false positive rate (1-specificity). A good ROC curve rises
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53 sharply, indicating a high proportion in true positive and a low proportion of false positives. The
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3 ROC curve for the GPRI was 0.78, which is considered as an indicator of an adequate screening
4 instrument [39].
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8 An important purpose of the GRPI in our study was to identify individuals at risk for post
9 genetic testing psychological distress. Therefore, the cutoff value was set to maximize
10 sensitivity – in another word, not to miss detecting a “case”. Using a GPRI cut off score of 50,
11 the instrument was able to predict 84% of the “cases” identified by HAM-D or HAM-A
12 conducted post genetic testing results, with a specificity value of 60% (Figure 1).
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27 **DISCUSSION**

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29 The aim of this study was to develop a brief, easy-to-use psychosocial screening instrument
30 specific for the genetic testing context and to examine its reliability and validity (Appendix A).
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32 To our knowledge this is the first report of a psychosocial screening instrument for use across
33 AOHD. Unlike current psychological instruments used mainly in research studies in genetics
34 clinics to identify existing symptoms of depression and anxiety, or impacts, the GPRI assesses
35 psychological risk factors, such as anticipated impacts of a genetic testing result and the
36 perception of the disease. The GPRI demonstrates promising psychometric properties as a tool
37 designed to assist genetics health care providers determine which of their patients undergoing
38 genetic testing for AOHD is at increased psychological risk and who will benefit from added
39 psychosocial support.
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53 A high reliability was demonstrated by a Cronbach's Alpha at 0.81, moderate to high
54 item-total correlation and inter-item correlation of the whole scale. The construct validity of the
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3 scale was supported by high correlations between the GPRI and standardized psychological
4 measures (BSI, IES). The clinical utility and predictive value of the GPRI was supported as
5 well. A GPRI score above the cutoff of 50 at baseline was able to predict 84% of “distress” cases
6 identified by HAM-D or HAM-A, a strong indicator of its potential usefulness in a clinical
7 setting.
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11 A brief self-administered screening questionnaire will be easy to incorporate into genetics
12 clinics; the GPRI can be completed and scored quickly during clinical visits and without
13 additional burden to patients and health providers. In addition, by focusing specifically on known
14 risk factors associated with inheritable illness, the instrument will be perceived as being more
15 clinically relevant and acceptable to patients. Patients with higher scores on the GPRI can be
16 flagged and either receive telephone follow up to further assess concerns or potential distress, or
17 be invited back for an appointment for further assessment treatment.
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32 Alternatively, genetic counselors or geneticists with available psychosocial personnel
33 could make a referral for a more formal psychosocial assessment to further explore and address
34 the specific psychological factors self-reported. For example, in the case where an individual is
35 particularly fearful of developing an illness or is concerned about specific impacts, such as
36 expecting relationship or family communications difficulties, or for those with a past history of
37 psychological illness, a psychologically trained health professional could employ cognitive-
38 behavioral strategies to address ongoing anxiety, or provide psychological treatment to address
39 any psychiatric symptoms (i.e. depression) [40]. Furthermore, several items incorporate
40 variables related to heritable disease experiences or their perceptions, and the scale appeared
41 acceptable to patients, demonstrating face validity in such a way that it may be more user
42 friendly for the non-mental health professional, compared for example, to a standardized
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3 psychological instrument on depression. The GPRI could be considered a “communimetric
4 measures”, that is, the items themselves are useful for the clinician in communicating concerns
5 about specific areas of functioning directly with the patient. For example, if item 6 is endorsed
6 by the patient as “strongly agree”, the clinician can further explore the patient’s concern and help
7 identify the need for further clinical services [41].
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15 Left untreated, significant levels of distress may lead to lower quality of life [40], or
16 potentially lower satisfaction with genetics services [21]. A screening approach allows both for
17 careful monitoring during a known stressful period-that of awaiting test results [42], and an
18 opportunity for planned follow up and optimal use of limited psychosocial resources [2, 20, 21].
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25 Our study findings are limited by the characteristics of the sample, in that most
26 participants were female and undergoing testing for *BRCA1/2*. This pattern is similar to that
27 observed in the literature on genetic testing for AOHD, which is predominantly focused on
28 Hereditary Breast-Ovarian Cancer Syndrome. We attempted to obtain a larger sample of
29 individuals undergoing genetic testing for HD or Lynch Syndrome which would presumably
30 provide a greater sample of males. However, these sample pools were much smaller. This study
31 and the GPRI represents a start to developing a general tool, since our belief and the literature
32 suggests that these mental health issues or adjustment risk factors are not disease specific. We
33 suggest that future studies address the validity of GPRI in male populations and in the rare adult
34 onset hereditary diseases, such as HD. Future studies should also include randomized controlled
35 trials to assess the effectiveness of the GPRI in predicting distress, the impact of the instrument
36 on referral patterns, patient and provider satisfaction, and provider knowledge and skill in
37 identifying and managing psychosocial distress, and on cost-effectiveness. The GPRI will also
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3 need to be evaluated in primary care settings where genetics services might be offered more
4 frequently to meet the demand.
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10 **CONCLUSIONS**

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

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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.

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Ms. Melyssa Aronson

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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.

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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.

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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	85 (12%)
	Female	627 (88%)
Type of AOHD being tested: n (%)	Cancer (BRCA)	580 (82%)
	Cancer (other, ie, Colon)	90 (13%)
	Huntington disease	31 (4%)
	Hemochromatosis	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

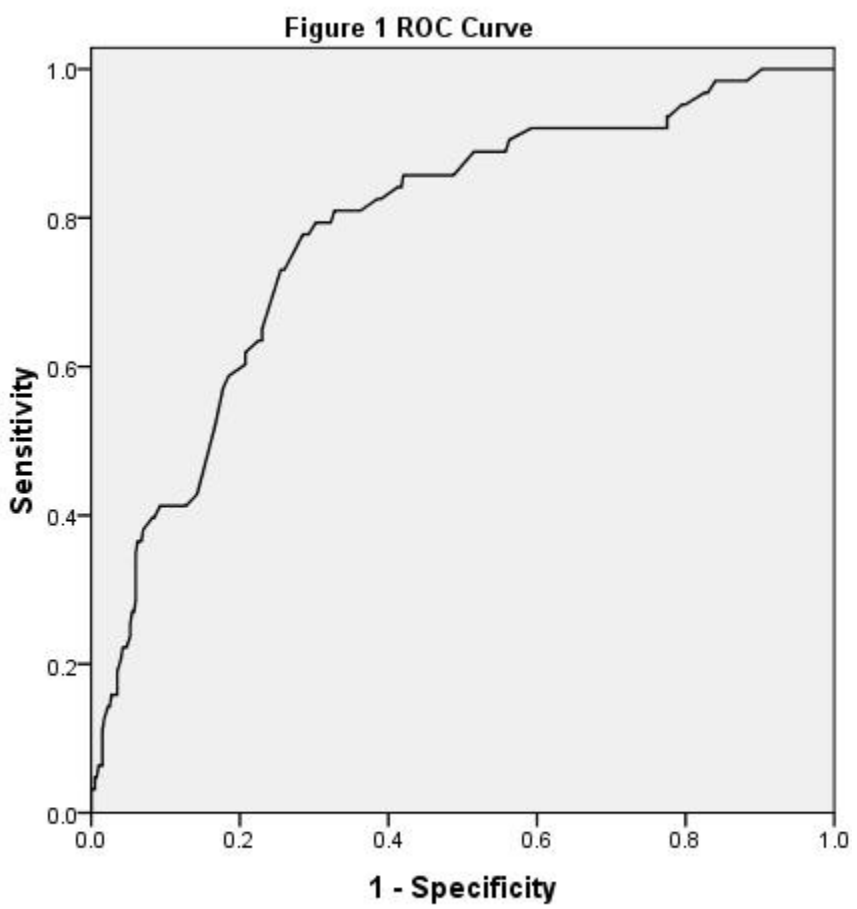
Table 2
Psychosocial Well Being 1 Month Post Genetic Testing Results
By Disease Type (N=473)

	Overall N (%)	Huntington	BRCA	Other Cancer
IES intrusion $\geq 17^a$	60 (13.0%)	5 (23.8%)	51 (12.5%)	4 (9.5%)
IES avoidance $\geq 17^a$	65 (13.7%)	5 (23.8%)	57 (14.0%)	3 (7.1%)
BSI-18 total $\geq 13^b$	95 (20.1%)	6 (28.6%)	86 (21.1%)	3 (7.1%)
<p>a. Shemesh E. et al (2004) Posttraumatic stress, non adherence, and adverse outcome in survivors of a myocardial infarction. <i>Psychosomatic Medicine</i>, 66: 521-526</p> <p>b. Zabora et al (2001): A new psychosocial screening instrument for use with cancer patients. <i>Psychosomatics</i>, 42:241–246</p>				

Table 3
GPRI Factor Solutions and Factor Loadings

	Factor Loadings	Communalities	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%				

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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):
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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 <u>have</u> 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 <u>currently</u> 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.

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

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Title

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

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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

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3 higher prevalence levels [6, 7].
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6 The risk factors for psychological symptoms amongst individuals undergoing genetic
7 testing have been delineated in several studies [4, 8, 9]. While there is generally elevated
8 distress using global measures for depression or anxiety among those who receive positive test
9 results [9-11], individuals testing negative or receiving uninformative results may also have
10 adjustment difficulties [12]. For example, individuals may feel guilt or continue to worry about
11 their disease risk [2, 7, 12]. These findings highlight the importance of considering risk factors
12 in addition to the test result itself. Individuals who have elevated psychological symptoms at the
13 pre-test stage and those with a previous psychiatric history (i.e., depression) are particularly at
14 risk for an adverse psychological outcome after testing [2, 8, 9].
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27 Additional risk factors for distress are more specific to the genetics context and include
28 the level of penetrance of the gene mutation or degree of certainty of developing the disease [4].
29 The perception of control over the disease (including the number of prevention/treatment
30 options) and perception of the immediacy of risk (proximity in age to perceived disease onset)
31 are important predictors [4, 13]. The expectation of a negative test result can play a role in
32 adjustment, as can the context of test results of other family members [9, 14]. As in other
33 medical areas, specific coping styles can affect adjustment [15]. The prior experiences with loss
34 of family members to disease, as well as the developmental level (i.e. young age) of the
35 individual at the time of the loss [2, 3, 16] are significant factors affecting potential adjustment.
36 In addition, the prior experience of giving care to a family member with the disease and lower
37 levels of social support have been associated with poorer adjustment following a positive test
38 result [2-4, 8, 16].
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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

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3 associated with heritable disease or genetic testing or risk, which may pose barriers for use by
4 genetics health service providers who may prefer instruments that, at face value, appear to them
5 and their patients as being clinically more relevant to the genetic testing context.
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10 More recently, new outcome measures designed to assess the psychological impact of
11 receiving genetic information have been developed. For example, the Multidimensional Impact
12 of Cancer Risk Assessment (MICRA) is designed to assess concerns and impacts associated with
13 genetic testing for BRCA1/2 [19] and another tool, the Psychological Adaptation to Genetic
14 Information Scale, is now available [23]. While these measures will require further validation
15 they provide more clinically relevant approaches to capturing specific impacts of genetic
16 information, such as the increased sense of vulnerability often experienced following genetic
17 testing [19, 23].
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29 Measures of global psychological functioning and the evolving outcome measurement
30 tools for the genetics field are not designed to “predict” vulnerability for future distress, but
31 rather, measure current distress levels. Screening, the aim of the tool developed in this study in
32 contrast, is a rapid, cost-effective alternative [21] to prospectively identify individuals who may
33 experience significant difficulty in their attempts to adapt to their genetic information [17]. A
34 screening tool enables providers to offer timely and focused educational and psychosocial
35 interventions to *prevent* future distress.
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46 The primary *objective* of this study was to develop a brief, reliable and valid
47 psychological risk screening instrument for use in the genetic testing context. The new
48 instrument aimed to incorporate empirically based risk factors for psychological symptoms and
49 would need to show a high sensitivity, specificity and predictive validity indicating risk for
50 future distress post genetic testing results. A cutoff point would need to be determined to guide
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3 clinical decisions as to whether or not to refer, further assess, or intervene to reduce an
4 individual's expressed concern.
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10 **METHODS AND MATERIALS**

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12 The study was carried out from September 2005 to July 2010, with research ethics board
13 approval from participating genetics clinics: Toronto (Mount Sinai Hospital, North York General
14 Hospital, Princess Margaret Hospital); Ottawa (Children's Hospital of Eastern Ontario); and
15 Vancouver (British Columbia Cancer Agency). Individuals beginning the genetic testing process
16 for AOHD at each site were approached by genetic counsellors on the project team for their
17 permission to be contacted about the study. Those who expressed interest were mailed the
18 baseline package that included the informed consent. The informed consent included all
19 components of the study, including questionnaires, follow-up phone calls, telephone interviews,
20 as well as to the release of their genetic testing information to the research team.
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34 A two phase approach was used for this study: **Phase I: Item Generation and Refinement**,
35 and **Phase II: Validation**. The multi-stage method [24] takes validation into consideration at
36 each stage of scale development and has been used successfully in previous studies [25].
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43 **Phase I: Item Generation and Refinement.**

44 ***Item generation***

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46 To generate items for the Genetic Psychosocial Risk Instrument (GPRI), a literature search was
47 performed for the following AOHDs: Cancer (Hereditary Breast-Ovarian Cancer Syndrome/
48 Lynch Syndrome), Huntington Disease (HD), and Hemochromatosis. These diseases were
49 selected as they represented the majority of patients attending genetic clinics and had an
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3 associated available psychosocial literature for review. Databases including Cinahl (1982 to
4 2006), Medline (1966 to 2006), PsychInfo (1985 to 2006), and Pubmed (1985 to 2006) were
5 searched as well as hand search of references from major publications. Keywords included:
6 genetic screening, genetic testing, psychological, psychological well-being, psychological
7 adjustment, stress, adaptation, cancer worry, disease worry, and distress. Selection criteria for the
8 literature review included studies with a follow-up design or review articles. Each selected study
9 was reviewed by two reviewers on its quality of evidence and generalizability using a
10 standardized template. A total of 73 relevant studies were identified among the disease groups:
11 49 on cancer, 20 on HD, 2 on Hemochromatosis, and 2 described mixed conditions.
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25 Risk factors for psychological distress identified by the literature review provided the
26 basis for item generation. Items were written in a mixed format where respondents were asked
27 for their endorsement of each statement ranging from Yes/No for risk factors of binary nature, to
28 a 5-point likert-type scale for risk factors with stages in frequency and/or intensity. The
29 instrument items were further refined by 10 genetic service providers (3 geneticists, 4 genetic
30 counselors, 2 oncologists, 1 genetics nurse) rating items on *comprehension, readability, and*
31 *perceived clinical relevance* using a ten-point scale with 0 being "excellent/definitely relevant"
32 and 10 being "very poor/definitely not relevant". Risk factor items were removed if rated above
33 five by more than 3 providers. Providers were also asked to suggest additional risk factor items.
34 These suggestions were checked against the literature for empirical evidence. Following this
35 step, 7 volunteers undergoing genetic testing for AOHDs were recruited to try out the scale for
36 clarity, succinctness and relevance from the clients' perspectives. At this stage, the proposed
37 instrument consisted of 56 items: demographics (4 items); perceived risk (8 items); life events
38 and family history of the disease (8 items); perceived impact of carrying a mutation (9 items);
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3 family communication (6 items); disease specific concerns (5 items); optimism (3 items); social
4 support (3 items), pre-morbid functioning and previous psychiatric history (10 items).
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10 ***Item refinement:***

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12 Subjects: Following informed consent, a convenient sample of 141 participants who had given
13 blood for genetic tests at the Toronto and Ottawa sites completed the GPRI (using a three
14 patients per item ratio) to select the best items for the candidate scale. The participants were
15 middle aged (48.67 ± 13.29), mostly female (77%) testing for hereditary breast cancer, and many
16 (65%) had already suffered the onset of the illness.
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24 Scoring: To ensure that binary items carry an equal weight as the 5-point likert-type
25 items, a score of 5 was assigned to *Yes* and 1 to *No*. A score of 3 or mean-substitute was assigned
26 to *Not Applicable* to allow it to be counted in the total score. Reliability analysis was carried out
27 and a Cronbach's Alpha was set for .75 or higher for the scale to move to the next phase [26].
28 Any item with an item-total correlation less than .20 was identified for potential removal. Using
29 team consensus, a total of 19 items were removed, combined or substituted, resulting in a 37
30 item GPRI candidate scale at the end of phase I.
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43 **Phase II: Scale Validation**

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45 Subjects: Individuals undergoing genetic testing for one of the AOHDs in each of the five study
46 sites were invited to participate: 1) age 18 or above undergoing genetic testing for cancer, HD, or
47 Hemochromatosis; 2) fluent in English; and 3) residing within 1.5 hours driving distance from
48 study site. Although the onset of an AOHD was not an exclusion criterion, individuals in
49 advanced stages of the illness and / or who were unable to consent due to cognitive impairment
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3 were excluded. At baseline, participants were asked to complete a set of self-report
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5 questionnaires (e.g. Brief Symptom Inventory, etc.) described below within a one month period
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7 following the provision of a blood sample. For those who received a genetic test result,
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9 questionnaires were mailed within two weeks to one month of the disclosure of test result. These
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11 participants were also telephoned to complete the Hamilton Depression and Hamilton telephone-
12
13 based Anxiety Scales to further assess depressive and anxiety symptoms. .
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17 Materials: At baseline, three psychosocial measures were used: GPRI Candidate Scale
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19 from Phase I. To facilitate scoring of the scale by genetic providers, scores for response to each
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21 item on the GPRI were imbedded in the questionnaire, where clinicians could calculate a total
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23 score in less than 5 minutes. Brief Symptom Inventory (BSI) The BSI is a 53-item measure of
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25 psychological distress that contains three global scales i) depression, ii) anxiety and iii)
26
27 somatization [27]. It is widely used in medical and psychiatric populations to assess
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29 psychological functioning; Impact of Event Scale (IES): The IES is a 15-item, likert-style scale
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31 used to assess the experience of a specific stress response and is designed to be easily anchored
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33 in relation to a specific stressor or life event. As previously utilized in the genetics literature to
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35 assess genetic testing-related distress, the IES items were anchored in relation to the event of
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37 “the genetic test result”. The IES has two sub-scales: i) intrusive thoughts and feelings associated
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39 with the stressful life event, and ii) items associated with patterns of avoidance of certain
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41 thoughts, feelings, or situations [28].
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49 Measures at one month post genetic testing results included: the self -reports scales of the
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51 BSI, IES and each participant received a telephone call for the telephone-based Hamilton
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53 Depression 29-item Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A). The
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55 HAM-D evaluates depressed mood, vegetative and cognitive symptoms of depression, and
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3 comorbid anxiety symptoms [29]. The HAM-A quantifies the severity of anxiety
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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

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3 would be classified as “at risk” for future onset of adjustment difficulties. This would be
4 confirmed by a high HAM-D or HAM-A score or “case” during 1 month follow-up. Similarly,
5 those with a low GPRI score should receive low score in HAM-D or HAM-A as “non-cases”.
6
7 The predictive value of the GRPI, describing the number of test-positives (in our case, high
8 GPRI) who truly have the psychological condition (i.e. cases identified by HAM-D or HAM-A),
9 was tested by a Receiver Operating Characteristic (ROC) curve which visually plotted the true
10 positive rate (sensitivity) over false positive rate (1-specificity). We included cases to be
11 identified by either anxiety and/or depressive symptomatology as both have been reported in the
12 literature [8, 9].
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24 To address the issue of missing follow-up data in a cohort study, as suggested in the
25 literature [33], we tested the assumption that the sub sample with missing data had a similar
26 baseline exposure (similar GPRI) as the non-missing subsample by comparing baseline GPRI
27 between the participants and dropouts. This step assesses if there was systematic bias resulting
28 from the loss of information in the follow-up period.
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39 RESULTS

40 Participant characteristics

41 Study packages were mailed to 1129 individuals interested in hearing more about the study. Of
42 these individuals, 722 of them consented and 712 (98%) completed the GPRI. Most participants
43 were tested for the inheritable cancers, while a small percentage of participants were tested for
44 hemochromatosis and HD. Similar to phase I, phase II participants were mostly female, at mid-
45 life stage, and more than half had a past diagnosis of the disease (see table 1).
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3 Of the 712 participants, 85 (12%) did not receive genetic testing results at the scheduled
4 follow-up time and were not eligible for follow-up measures on psychological symptoms in
5 response to a genetic testing result. Of the remaining 627 participants, 152 (24%) did not return
6 the self-administered follow-up questionnaires and 12 (2%) submitted the follow-up
7 questionnaire package but did not complete a standardized telephone interview using HAM-D
8 and HAM-A (up to 4 telephone calls were made to reach each participant). Therefore the final
9 number of participants with complete follow-up data is 463 (74%). The age, and baseline GPRI
10 score between individuals who did not receive genetic testing results (age 51.4 ± 12.7 , GPRI
11 49.3 ± 12.7), those who did not return the follow-up questionnaires (age 48.1 ± 11.6 , GPRI
12 50.2 ± 14.4) and those who completed follow-up measures (age 50.1 ± 12.8 , GPRI 49.1 ± 13.5) were
13 compared. There was no statistically significant group difference (ANOVA and all post-hoc
14 comparisons $p > 0.05$).

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

18
19 We carried out the calculations for distress level, for example, for depression and anxiety
20 symptoms using the BSI data, for specific distress associated a genetic test result using the IES.
21 Approximately, 13.0% to 20.1% of participants reached the threshold of moderate to severe
22 distress respectively (see table 2).

23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

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

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

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12 A reliability analysis was performed on 37 items. Twenty items belonging to 18 questions were
13
14 selected based on the criteria for item selection described in the methods section. The
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16 Cronbach's alpha of the 20 item GPRI was 0.81 suggesting a good level of internal consistency.
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20 The factor analysis resulted in a psychometrically sound 3-factor solution, with subscales
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22 representing the dimensions of: 1) *Perceived impact and personal adjustment to genetic testing*
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24 (12 items); 2) *Past history of mental health concerns* (5 items) and 3) *Personal history/family*
25
26 *history/loss to cancer* (3 items). All three factors met the minimum Eigenvalue criteria of 1.
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30 The first, 12-item factor (ALPHA = 0.85), accounting for 22% of the variance, includes
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32 items associated with the anticipated or experienced impact of being at high risk for AOHD.
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34 Example items included: "My worries about the disease affect my daily mood"; "The disease for
35
36 which I am at risk is currently causing a significant disruption in my family life".
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40 The second 5-item factor (ALPHA = 0.76), accounted for an additional 14% of the total
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42 variance, and reflected a sense of a person's past history or vulnerability in the area of mental
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44 health , e.g. "I have had emotional problems in the past", These items have been used in other
45
46 medical health areas [37, 38] and tend to be predictive of maladjustment [20] following a life
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48 event.
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51 The third 3 item factor (ALPHA = 0.08), accounted for 8% of the total variance and
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53 pertained to personal or family-related experiences associated with the heritable disorder for
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55 which the participant is undergoing testing. . Examples include: "I have a personal diagnosis of
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3 the disease for which I am receiving counseling”; “I lost a close family member to the disease for
4 which I am receiving counseling”; and “I have taken care of a very ill parent or another close
5 family member”. These 3 final items had low item total correlation because they were different
6 from the rest of the items in that they focused on direct experiences related to the illness, rather
7 than psychosocial-related items. These items were kept in the scale as they contributed
8 significantly to the overall variance, and correlated highly with HAM-D and HAM-A. To
9 determine the relationships between the three factors/subscales, correlations were computed.
10 Factor1 and factor2 had moderate correlations with each other (factor1/factor2 $r=0.30$, $p<0.01$).
11 The correlation of the first two factors with factor3 was much lower as expected (factor1/factor3
12 $r=0.06$, and factor2/factor3 $r=0.01$, not statistically significant). These results support the
13 multidimensional character of the GPRI scale (see Table 3).
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30 **Insert Table 3 about Here**

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32 One additional statement “I am interested in talking to a counselor about one or more of
33 these concerns” was added to the tool at the end as suggested by participants and providers to
34 remind them the option of seeing a counselor if required. This statement is not part of the items
35 examined during the instrument development and therefore does not carry a score.
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41 The total score for the 20 item GPRI ranged from 20 to 100, with a sample mean
42 49.36 ± 13.23 . The total was calculated by the sum of the raw scores for each of the statements.
43 Females had a significantly higher score for the GPRI than males (50.37 ± 13.14 vs. 41.91 ± 11.47 ,
44 $p<0.01$), and participants testing for HD had a higher, but non-significant score than participants
45 testing for cancer (52.24 ± 13.24 vs. 49.37 ± 13.22 , n.s.).
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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. $47.91 \pm 12.27, p < 0.01$). Same patterns were observed for HAM-A high (N=40) vs. low (N=423) (62.53 ± 12.92 vs. $48.25 \pm 12.43, p < 0.01$).

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.

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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

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3 patients undergoing genetic testing for AOHD is at increased psychological risk and should
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5 likely be considered for additional psychosocial support to facilitate adjustment to a test result.
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8 A high reliability was demonstrated by a Cronbach's Alpha at 0.81, moderate to high
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10 item-total correlation and inter-item correlation of the whole scale. The construct validity of the
11
12 scale was supported by high correlations between the GPRI and standardized psychological
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14 measures (BSI, IES). The clinical utility and predictive value of the GPRI was supported as
15
16 well. A GPRI score above the cutoff of 50 at baseline was able to predict 84% of “distress” cases
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18 identified by HAM-D or HAM-A, a strong indicator of its potential usefulness in a clinical
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20 setting.
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24 A brief self-administered screening tool will be easy and likely highly acceptable for
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26 incorporation into genetics clinics. The GPRI can be completed and scored quickly during
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28 clinical visits and without additional burden to patients and health providers. In addition, by
29
30 focusing specifically on known risk factors associated with inheritable illness, the instrument
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32 will be perceived as being more clinically relevant and acceptable to patients. Patients with
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34 higher GPRI scores can be flagged and either receive telephone follow-up to further assess
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36 concerns or potential distress or be invited back for an appointment for further assessment and
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38 required psychological treatment.
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43 Alternatively, genetic clinics with available psychosocial personnel could utilize the tool
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45 to guide referrals for a formal psychosocial assessment that can further explore and address
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47 specific self-reported psychological factors. For example, in the case where an individual is
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49 particularly fearful of developing an illness or is concerned about specific impacts, such as
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51 expecting relationship or family communications difficulties, information on communication
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53 strategies, personal coaching or family-based interventions could be employed to support the
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3 individual. For an individuals who reports a past history of psychological illness, a mental health
4 professional could further assess current psychological functioning and implement specific
5 approaches, and could offer cognitive-behavioral strategies or psychotropic medication to assist
6 in the management of anxiety or depressive symptoms [40]. Several items incorporate variables
7 related to heritable disease experiences and associated perceptions which can be used to guide
8 educational interventions to correct any myths or beliefs.
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11 The scale appeared highly acceptable to patients. A high face validity will contribute to
12 better scale uptake being perceived as “user friendly” and clinically relevant, compared for
13 example, to a standardized psychological instrument on depression, which have demonstrated
14 some barriers to clinic uptake [19]. The GPRI in contrast might be considered as a
15 “communimetric measure”, that is, the items themselves are useful for the clinician in
16 communicating concerns about specific areas of functioning directly with the patient [41].
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19 Left untreated, significant levels of psychological symptoms may lead to lower quality
20 of life [40], and lower satisfaction with genetics services [21]. A psychological screening
21 approach allows both for careful monitoring during a known stressful period-that of awaiting test
22 results [42], and provides an opportunity for any planned follow-up care. Flagging those
23 individuals who might benefit most from psychosocial care also best utilizes the often limited
24 psychological resources in genetic clinics [2, 20, 21].
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27 Our study findings are limited by the characteristics of the sample, in that most
28 participants were female and undergoing testing for *BRCA1/2*. This pattern is similar to that
29 observed in the literature on genetic testing for AOHD, which is predominantly focused on
30 Hereditary Breast-Ovarian Cancer Syndrome. We attempted to obtain a larger sample of
31 individuals undergoing genetic testing for HD or Lynch Syndrome which would presumably
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3 provide a greater sample of males. However, these sample pools were much smaller. However,
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5 this study and the resulting GPRI represent an attempt to begin the development of a general tool
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7 that addresses concerns that are relevant across genetic samples. Our belief stemming from
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9 clinical practice and the associated literature suggest that the identified mental health issues or
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11 adjustment risk factors are not disease specific. We suggest that future studies further address the
12
13 validity of GPRI in male populations and in the rare adult onset hereditary diseases, such as HD.
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15 Future studies should also include randomized controlled trials to assess the effectiveness of the
16
17 GPRI in predicting distress, its impact on referral patterns, patient and provider satisfaction, as
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19 well as on cost-effectiveness. The GPRI could also be evaluated in primary care settings where
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21 genetics services might be offered more frequently to meet the demand.
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29 **CONCLUSIONS**

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

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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.

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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.

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Ms. Melyssa Aronson

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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.

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Title

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

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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

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3 higher prevalence levels [6, 7].
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6 The risk factors for psychological symptoms amongst individuals undergoing genetic
7 testing have been delineated in several studies [4, 8, 9]. While there is generally elevated
8 distress using global measures for depression or anxiety among those who receive positive test
9 results [9-11], individuals testing negative or receiving uninformative results may also have
10 adjustment difficulties [12]. For example, individuals may feel guilt or continue to worry about
11 their disease risk [2, 7, 12]. These findings highlight the importance of considering risk factors
12 in addition to the test result itself. Individuals who have elevated psychological symptoms at the
13 pre-test stage and those with a previous psychiatric history (i.e., depression) are particularly at
14 risk for an adverse psychological outcome after testing [2, 8, 9].
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27 Additional risk factors for distress are more specific to the genetics context and include
28 the level of penetrance of the gene mutation or degree of certainty of developing the disease [4].
29 The perception of control over the disease (including the number of prevention/treatment
30 options) and perception of the immediacy of risk (proximity in age to perceived disease onset)
31 are important predictors [4, 13]. The expectation of a negative test result can play a role in
32 adjustment, as can the context of test results of other family members [9, 14]. As in other
33 medical areas, specific coping styles can affect adjustment [15]. The prior experiences with loss
34 of family members to disease, as well as the developmental level (i.e. young age) of the
35 individual at the time of the loss [2, 3, 16] are significant factors affecting potential adjustment.
36 In addition, the prior experience of giving care to a family member with the disease and lower
37 levels of social support have been associated with poorer adjustment following a positive test
38 result [2-4, 8, 16].
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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

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3 associated with heritable disease or genetic testing or risk, which may pose barriers for use by
4 genetics health service providers who may prefer instruments that, at face value, appear to them
5 and their patients as being clinically more relevant to the genetic testing context.
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10 More recently, new outcome measures designed to assess the psychological impact of
11 receiving genetic information have been developed. For example, the Multidimensional Impact
12 of Cancer Risk Assessment (MICRA) is designed to assess concerns and impacts associated with
13 genetic testing for BRCA1/2 [19] and another tool, the Psychological Adaptation to Genetic
14 Information Scale, is now available [23]. While these measures will require further validation
15 they provide more clinically relevant approaches to capturing specific impacts of genetic
16 information, such as the increased sense of vulnerability often experienced following genetic
17 testing [19, 23].
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29 Measures of global psychological functioning and the evolving outcome measurement
30 tools for the genetics field are not designed to “predict” vulnerability for future distress, but
31 rather, measure current distress levels. Screening, the aim of the tool developed in this study in
32 contrast, is a rapid, cost-effective alternative [21] to prospectively identify individuals who may
33 experience significant difficulty in their attempts to adapt to their genetic information [17]. A
34 screening tool enables providers to offer timely and focused educational and psychosocial
35 interventions to *prevent* future distress.
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46 The primary *objective* of this study was to develop a brief, reliable and valid
47 psychological risk screening instrument for use in the genetic testing context. The new
48 instrument aimed to incorporate empirically based risk factors for psychological symptoms and
49 would need to show a high sensitivity, specificity and predictive validity indicating risk for
50 future distress post genetic testing results. A cutoff point would need to be determined to guide
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3 clinical decisions as to whether or not to refer, further assess, or intervene to reduce an
4 individual's expressed concern.
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10 **METHODS AND MATERIALS**

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12 The study was carried out from September 2005 to July 2010, with research ethics board
13 approval from participating genetics clinics: Toronto (Mount Sinai Hospital, North York General
14 Hospital, Princess Margaret Hospital); Ottawa (Children's Hospital of Eastern Ontario); and
15 Vancouver (British Columbia Cancer Agency). Individuals beginning the genetic testing process
16 for AOHD at each site were approached by genetic counsellors on the project team for their
17 permission to be contacted about the study. Those who expressed interest were mailed the
18 baseline package that included the informed consent. The informed consent included all
19 components of the study, including questionnaires, follow-up phone calls, telephone interviews,
20 as well as to the release of their genetic testing information to the research team.
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34 A two phase approach was used for this study: **Phase I: Item Generation and Refinement**,
35 and **Phase II: Validation**. The multi-stage method [24] takes validation into consideration at
36 each stage of scale development and has been used successfully in previous studies [25].
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43 **Phase I: Item Generation and Refinement.**

44 ***Item generation***

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46 To generate items for the Genetic Psychosocial Risk Instrument (GPRI), a literature search was
47 performed for the following AOHDs: Cancer (Hereditary Breast-Ovarian Cancer Syndrome/
48 Lynch Syndrome), Huntington Disease (HD), and Hemochromatosis. These diseases were
49 selected as they represented the majority of patients attending genetic clinics and had an
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3 associated available psychosocial literature for review. Databases including Cinahl (1982 to
4 2006), Medline (1966 to 2006), PsychInfo (1985 to 2006), and Pubmed (1985 to 2006) were
5 searched as well as hand search of references from major publications. Keywords included:
6 genetic screening, genetic testing, psychological, psychological well-being, psychological
7 adjustment, stress, adaptation, cancer worry, disease worry, and distress. Selection criteria for the
8 literature review included studies with a follow-up design or review articles. Each selected study
9 was reviewed by two reviewers on its quality of evidence and generalizability using a
10 standardized template. A total of 73 relevant studies were identified among the disease groups:
11 49 on cancer, 20 on HD, 2 on Hemochromatosis, and 2 described mixed conditions.
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24 Risk factors for psychological distress identified by the literature review provided the
25 basis for item generation. Items were written in a mixed format where respondents were asked
26 for their endorsement of each statement ranging from Yes/No for risk factors of binary nature, to
27 a 5-point likert-type scale for risk factors with stages in frequency and/or intensity. The
28 instrument items were further refined by 10 genetic service providers (3 geneticists, 4 genetic
29 counselors, 2 oncologists, 1 genetics nurse) rating items on *comprehension, readability, and*
30 *perceived clinical relevance* using a ten-point scale with 0 being "excellent/definitely relevant"
31 and 10 being "very poor/definitely not relevant". Risk factor items were removed if rated above
32 five by more than 3 providers. Providers were also asked to suggest additional risk factor items.
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3 family communication (6 items); disease specific concerns (5 items); optimism (3 items); social
4 support (3 items), pre-morbid functioning and previous psychiatric history (10 items).
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10 ***Item refinement:***

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12 Subjects: Following informed consent, a convenient sample of 141 participants who had given
13 blood for genetic tests at the Toronto and Ottawa sites completed the GPRI (using a three
14 patients per item ratio) to select the best items for the candidate scale. The participants were
15 middle aged (48.67 ± 13.29), mostly female (77%) testing for hereditary breast cancer, and many
16 (65%) had already suffered the onset of the illness.
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24 Scoring: To ensure that binary items carry an equal weight as the 5-point likert-type
25 items, a score of 5 was assigned to *Yes* and 1 to *No*. A score of 3 or mean-substitute was assigned
26 to *Not Applicable* to allow it to be counted in the total score. Reliability analysis was carried out
27 and a Cronbach's Alpha was set for .75 or higher for the scale to move to the next phase [26].
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44 **Phase II: Scale Validation**

46 Subjects: Individuals undergoing genetic testing for one of the AOHDs in each of the five study
47 sites were invited to participate: 1) age 18 or above undergoing genetic testing for cancer, HD, or
48 Hemochromatosis; 2) fluent in English; and 3) residing within 1.5 hours driving distance from
49 study site. Although the onset of an AOHD was not an exclusion criterion, individuals in
50 advanced stages of the illness and / or who were unable to consent due to cognitive impairment
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3 were excluded. At baseline, participants were asked to complete a set of self-report
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5 questionnaires (e.g. Brief Symptom Inventory, etc.) described below within a one month period
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7 following the provision of a blood sample. For those who received a genetic test result,
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9 questionnaires were mailed within two weeks to one month of the disclosure of test result. These
10
11 participants were also telephoned to complete the Hamilton Depression and Hamilton telephone-
12
13 based Anxiety Scales to further assess depressive and anxiety symptoms. .
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17 Materials: At baseline, three psychosocial measures were used: GPRI Candidate Scale
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19 from Phase I. To facilitate scoring of the scale by genetic providers, scores for response to each
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21 item on the GPRI were imbedded in the questionnaire, where clinicians could calculate a total
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23 score in less than 5 minutes. Brief Symptom Inventory (BSI) The BSI is a 53-item measure of
24
25 psychological distress that contains three global scales i) depression, ii) anxiety and iii)
26
27 somatization [27]. It is widely used in medical and psychiatric populations to assess
28
29 psychological functioning; Impact of Event Scale (IES): The IES is a 15-item, likert-style scale
30
31 used to assess the experience of a specific stress response and is designed to be easily anchored
32
33 in relation to a specific stressor or life event. As previously utilized in the genetics literature to
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35 assess genetic testing-related distress, the IES items were anchored in relation to the event of
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37 “the genetic test result”. The IES has two sub-scales: i) intrusive thoughts and feelings associated
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39 with the stressful life event, and ii) items associated with patterns of avoidance of certain
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41 thoughts, feelings, or situations [28].
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49 Measures at one month post genetic testing results included: the self -reports scales of the
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51 BSI, IES and each participant received a telephone call for the telephone-based Hamilton
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53 Depression 29-item Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A). The
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55 HAM-D evaluates depressed mood, vegetative and cognitive symptoms of depression, and
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3 comorbid anxiety symptoms [29]. The HAM-A quantifies the severity of anxiety
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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

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3 would be classified as “at risk” for future onset of adjustment difficulties. This would be
4 confirmed by a high HAM-D or HAM-A score or “case” during 1 month follow-up. Similarly,
5 those with a low GPRI score should receive low score in HAM-D or HAM-A as “non-cases”.
6
7 The predictive value of the GRPI, describing the number of test-positives (in our case, high
8 GPRI) who truly have the psychological condition (i.e. cases identified by HAM-D or HAM-A),
9 was tested by a Receiver Operating Characteristic (ROC) curve which visually plotted the true
10 positive rate (sensitivity) over false positive rate (1-specificity). We included cases to be
11 identified by either anxiety and/or depressive symptomatology as both have been reported in the
12 literature [8, 9].
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25 To address the issue of missing follow-up data in a cohort study, as suggested in the
26 literature [33], we tested the assumption that the sub sample with missing data had a similar
27 baseline exposure (similar GPRI) as the non-missing subsample by comparing baseline GPRI
28 between the participants and dropouts. This step assesses if there was systematic bias resulting
29 from the loss of information in the follow-up period.
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39 RESULTS

40 Participant characteristics

41 Study packages were mailed to 1129 individuals interested in hearing more about the study. Of
42 these individuals, 722 of them consented and 712 (98%) completed the GPRI. Most participants
43 were tested for the inheritable cancers, while a small percentage of participants were tested for
44 hemochromatosis and HD. Similar to phase I, phase II participants were mostly female, at mid-
45 life stage, and more than half had a past diagnosis of the disease (see table 1).
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55 **Insert Table 1 about Here**
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3 Of the 712 participants, 85 (12%) did not receive genetic testing results at the scheduled
4 follow-up time and were not eligible for follow-up measures on psychological symptoms in
5 response to a genetic testing result. Of the remaining 627 participants, 152 (24%) did not return
6 the self-administered follow-up questionnaires and 12 (2%) submitted the follow-up
7 questionnaire package but did not complete a standardized telephone interview using HAM-D
8 and HAM-A (up to 4 telephone calls were made to reach each participant). Therefore the final
9 number of participants with complete follow-up data is 463 (74%). The age, and baseline GPRI
10 score between individuals who did not receive genetic testing results (age 51.4±12.7, GPRI
11 49.3±12.7), those who did not return the follow-up questionnaires (age 48.1±11.6, GPRI
12 50.2±14.4) and those who completed follow-up measures (age 50.1±12.8, GPRI 49.1±13.5) were
13 compared. There was no statistically significant group difference (ANOVA and all post-hoc
14 comparisons $p>0.05$).

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

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

22 **Insert Table 2 about Here**

23 HAM-D and HAM-A interview data from 463 participants were used as a further
24 validation tool to measure psychological symptoms post genetic testing results. Defined by cut-
25 offs for HAM-D ≥ 12 [35] or HAM-A ≥ 10 in the literature [36], the rates for psychological
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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 hereditary disorder for which the participant is undergoing testing. Examples include: "I have a personal diagnosis of

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3 the disease for which I am receiving counseling”; “I lost a close family member to the disease for
4 which I am receiving counseling”; and “I have taken care of a very ill parent or another close
5 family member”. These 3 final items had low item total correlation because they were different
6 from the rest of the items in that they focused on direct experiences related to the illness, rather
7 than psychosocial-related items. These items were kept in the scale as they contributed
8 significantly to the overall variance, and correlated highly with HAM-D and HAM-A. To
9 determine the relationships between the three factors/subscales, correlations were computed.
10 Factor1 and factor2 had moderate correlations with each other (factor1/factor2 $r=0.30$, $p<0.01$).
11 The correlation of the first two factors with factor3 was much lower as expected (factor1/factor3
12 $r=0.06$, and factor2/factor3 $r=0.01$, not statistically significant). These results support the
13 multidimensional character of the GPRI scale (see Table 3).
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32 One additional statement “I am interested in talking to a counselor about one or more of
33 these concerns” was added to the tool at the end as suggested by participants and providers to
34 remind them the option of seeing a counselor if required. This statement is not part of the items
35 examined during the instrument development and therefore does not carry a score.
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41 The total score for the 20 item GPRI ranged from 20 to 100, with a sample mean
42 49.36 ± 13.23 . The total was calculated by the sum of the raw scores for each of the statements.
43 Females had a significantly higher score for the GPRI than males (50.37 ± 13.14 vs. 41.91 ± 11.47 ,
44 $p<0.01$), and participants testing for HD had a higher, but non-significant score than participants
45 testing for cancer (52.24 ± 13.24 vs. 49.37 ± 13.22 , n.s.).
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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. $47.91 \pm 12.27, p < 0.01$). Same patterns were observed for HAM-A high (N=40) vs. low (N=423) (62.53 ± 12.92 vs. $48.25 \pm 12.43, p < 0.01$).

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.

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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

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3 patients undergoing genetic testing for AOHD is at increased psychological risk and should
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5 likely be considered for additional psychosocial support to facilitate adjustment to a test result.
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8 A high reliability was demonstrated by a Cronbach's Alpha at 0.81, moderate to high
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10 item-total correlation and inter-item correlation of the whole scale. The construct validity of the
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12 scale was supported by high correlations between the GPRI and standardized psychological
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14 measures (BSI, IES). The clinical utility and predictive value of the GPRI was supported as
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16 well. A GPRI score above the cutoff of 50 at baseline was able to predict 84% of “distress” cases
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18 identified by HAM-D or HAM-A, a strong indicator of its potential usefulness in a clinical
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20 setting.
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24 A brief self-administered screening tool will be easy and likely highly acceptable for
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26 incorporation into genetics clinics. The GPRI can be completed and scored quickly during
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28 clinical visits and without additional burden to patients and health providers. In addition, by
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30 focusing specifically on known risk factors associated with inheritable illness, the instrument
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32 will be perceived as being more clinically relevant and acceptable to patients. Patients with
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34 higher GPRI scores can be flagged and either receive telephone follow-up to further assess
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36 concerns or potential distress or be invited back for an appointment for further assessment and
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38 required psychological treatment.
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43 Alternatively, genetic clinics with available psychosocial personnel could utilize the tool
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45 to guide referrals for a formal psychosocial assessment that can further explore and address
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47 specific self-reported psychological factors. For example, in the case where an individual is
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49 particularly fearful of developing an illness or is concerned about specific impacts, such as
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51 expecting relationship or family communications difficulties, **information on communication**
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53 **strategies, personal coaching or family-based interventions could be employed to support the**
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3 individual. For an individuals who reports a past history of psychological illness, a mental health
4 professional could further assess current psychological functioning and implement specific
5 approaches, and could offer cognitive-behavioral strategies or psychotropic medication to assist
6 in the management of anxiety or depressive symptoms [40]. Several items incorporate variables
7 related to heritable disease experiences and associated perceptions which can be used to guide
8 educational interventions to correct any myths or beliefs.
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18 The scale appeared highly acceptable to patients. A high face validity will contribute to
19 better scale uptake being perceived as “user friendly” and clinically relevant, compared for
20 example, to a standardized psychological instrument on depression, which have demonstrated
21 some barriers to clinic uptake [19]. The GPRI in contrast might be considered as a
22 “communimetric measure”, that is, the items themselves are useful for the clinician in
23 communicating concerns about specific areas of functioning directly with the patient [41].
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32 Left untreated, significant levels of psychological symptoms may lead to lower quality
33 of life [40], and lower satisfaction with genetics services [21]. A psychological screening
34 approach allows both for careful monitoring during a known stressful period-that of awaiting test
35 results [42], and provides an opportunity for any planned follow-up care. Flagging those
36 individuals who might benefit most from psychosocial care also best utilizes the often limited
37 psychological resources in genetic clinics [2, 20, 21].
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47 Our study findings are limited by the characteristics of the sample, in that most
48 participants were female and undergoing testing for *BRCA1/2*. This pattern is similar to that
49 observed in the literature on genetic testing for AOHD, which is predominantly focused on
50 Hereditary Breast-Ovarian Cancer Syndrome. We attempted to obtain a larger sample of
51 individuals undergoing genetic testing for HD or Lynch Syndrome which would presumably
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3 provide a greater sample of males. However, these sample pools were much smaller. However,
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5 this study and the resulting GPRI represent an attempt to begin the development of a general tool
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7 that addresses concerns that are relevant across genetic samples. Our belief stemming from
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9 clinical practice and the associated literature suggest that the identified mental health issues or
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11 adjustment risk factors are not disease specific. We suggest that future studies further address the
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13 validity of GPRI in male populations and in the rare adult onset hereditary diseases, such as HD.
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15 Future studies should also include randomized controlled trials to assess the effectiveness of the
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17 GPRI in predicting distress, its impact on referral patterns, patient and provider satisfaction, as
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19 well as on cost-effectiveness. The GPRI could also be evaluated in primary care settings where
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21 genetics services might be offered more frequently to meet the demand.
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29 CONCLUSIONS

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

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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.

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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%)

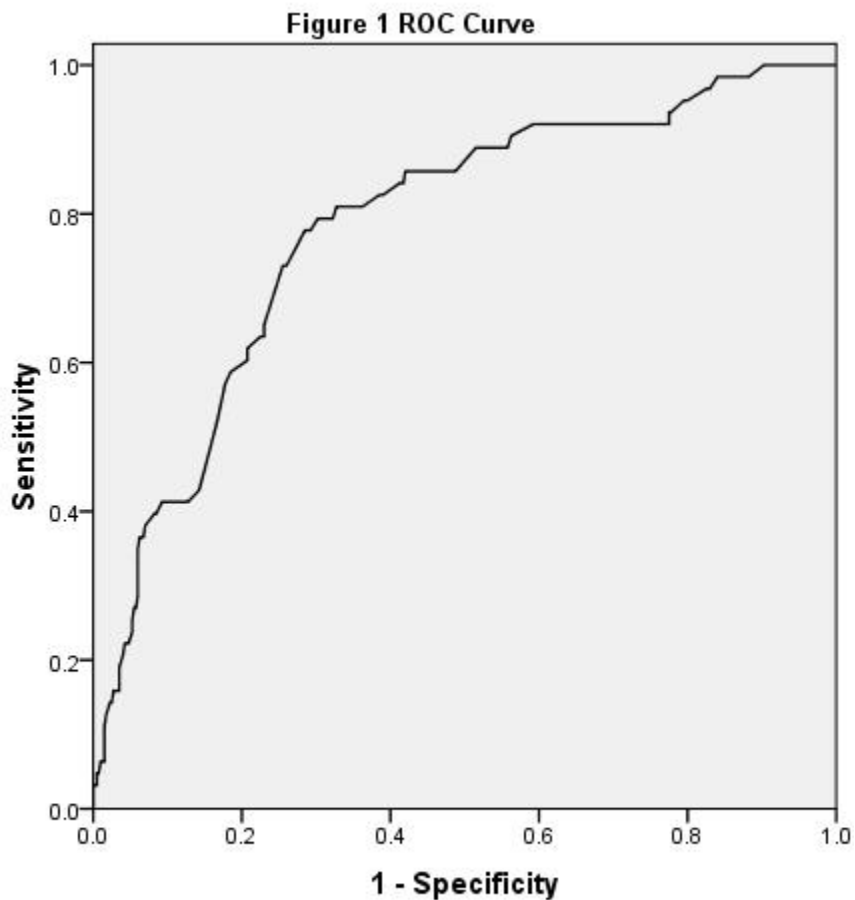
* Note: there are missing data for some GRPI variables. The total count for each variable do not necessarily add up to 712

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 $\geq 17^a$	60 (13.0%)	5 (23.8%)	51 (12.5%)	4 (9.5%)
IES avoidance $\geq 17^a$	65 (13.7%)	5 (23.8%)	57 (14.0%)	3 (7.1%)
BSI-18 total $\geq 13^b$	95 (20.1%)	6 (28.6%)	86 (21.1%)	3 (7.1%)
<p>a. Shemesh E. et al (2004) Posttraumatic stress, non adherence, and adverse outcome in survivors of a myocardial infarction. <i>Psychosomatic Medicine</i>, 66: 521-526</p> <p>b. Zabora et al (2001): A new psychosocial screening instrument for use with cancer patients. <i>Psychosomatics</i>, 42:241-246</p>				

Table 3
GPRI Factor Solutions and Factor Loadings

	Factor Loadings	Communalities	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%				



36 Diagonal segments are produced by ties.

For peer review only

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):

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|--|-----------|----------|
| 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 |
| <u>If yes</u> , 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 |
| <u>If yes</u> , 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 <u>have</u> 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 <u>currently</u> 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.

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

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Title

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

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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 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.

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3 instruments measuring breast/ovarian cancer worry) have demonstrated higher prevalence levels
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5 [6, 7].
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8 The risk factors for psychological symptoms amongst individuals undergoing genetic
9 testing have been delineated in several studies [4, 8, 9]. While there is generally elevated
10 distress using global measures for depression or anxiety among those who receive positive test
11 results [9-11], individuals testing negative or receiving uninformative results may also have
12 adjustment difficulties [12] following testing. For example, individuals may feel guilt or
13 continue to worry about their disease risk even when testing negative [2, 7, 12]. These findings
14 highlight the importance of considering risk factors in addition to the type of test result itself.
15 Individuals who have elevated psychological symptoms at the pre-test stage and those with a
16 previous psychiatric history (i.e., depression) are particularly at risk for an adverse psychological
17 outcome after testing [2, 8, 9].
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32 Additional risk factors for distress are more specific to the genetics context and include
33 the level of penetrance of the gene mutation or degree of certainty of developing the disease [4].
34 The perception of control over the disease (including the number of prevention/treatment
35 options) and perception of the immediacy of risk (proximity in age to perceived disease onset)
36 are important predictors [4, 13]. The expectation of a negative test result can play a role in
37 adjustment, as can the context of test results of other family members [9, 14]. As in other
38 medical areas, specific coping styles can affect adjustment [15]. The prior experiences with loss
39 of family members to disease, as well as the developmental level (i.e. young age) of the
40 individual at the time of the loss [2, 3, 16] are significant factors affecting potential adjustment.
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53 In addition, the prior experience of giving care to a family member with the disease and lower
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3 levels of social support have been associated with poorer adjustment following a positive test
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5 result [2-4, 8, 16].
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8 It is clear that there is not one predominant factor, but rather, a series of variables that can
9
10 be assessed prior to receiving a test result that may contribute to elevated levels of psychological
11
12 distress following genetic testing [2, 17]. Emotional reactions may impede the assimilation of
13
14 risk information and the adoption of preventive measures recommended following notification of
15
16 a mutation [2, 18]. Psychological distress occurs along a continuum [19, 20] and can be difficult
17
18 to identify by health professionals [21]. Distress may not become manifest to the health care
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20 team until the patient reaches an observable crisis level, i.e. the onset of severe depression or
21
22 anxiety, or significant conflicts with the family. An early screening instrument would enable
23
24 healthcare providers to identify patients being at higher psychological risk in order that
25
26 appropriate support can be given at the right time. In fact, there is now a general consensus that
27
28 genetic testing should be accompanied by psychological support to promote optimal adjustment
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30 [2, 22].
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39 **Screening for Psychological Risk Factors- Why is it necessary?**

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41 The gold standard for identifying psychologically distressed individuals involves structured
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43 clinical interviews administered by a clinical psychologist or psychiatrist [21]. However, it is too
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45 costly and often not feasible in genetic clinics. Standardized measures of psychological
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47 functioning (e.g. global scales of depression or anxiety) can also be used as a method for
48
49 identifying distress. However, few clinics use these measures in practice because of personnel
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51 and time requirements for scoring and interpretation of them. Furthermore, items on these
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53 measures typically focus on symptoms of anxiety or depression, rather than on variables
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3 associated with heritable disease or genetic testing or risk, which may pose barriers for use by
4 genetics health service providers who may prefer instruments that, at face value, appear to them
5 and their patients as being clinically more relevant to the genetic testing context.
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10 More recently, new outcome measures designed to assess the psychological impact of
11 receiving genetic information have been developed. For example, the Multidimensional Impact
12 of Cancer Risk Assessment (MICRA) is designed to assess concerns and impacts associated with
13 genetic testing for BRCA1/2 [19] and another tool, the Psychological Adaptation to Genetic
14 Information Scale, is now available [23]. While these measures will require further validation
15 they provide more clinically relevant approaches to capturing specific impacts of genetic
16 information, such as the increased sense of vulnerability often experienced following genetic
17 testing [19, 23].
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29 Measures of global psychological functioning and the evolving outcome measurement
30 tools for the genetics field are not designed to “predict” vulnerability for future distress, but
31 rather, measure current distress levels. Screening, the aim of the tool developed in this study in
32 contrast, is a rapid, cost-effective alternative [21] to prospectively identify individuals who may
33 experience significant difficulty in their attempts to adapt to their genetic information [17]. A
34 screening tool enables providers to offer timely and focused educational and psychosocial
35 interventions to *prevent* future distress.
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46 The primary *objective* of this study was to develop a brief, reliable and valid
47 psychological risk screening instrument for use in the genetic testing context. The new
48 instrument aimed to incorporate empirically based risk factors for psychological symptoms and
49 would need to show a high sensitivity, specificity and predictive validity indicating risk for
50 future distress post genetic testing results. A cutoff point would need to be determined to guide
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3 clinical decisions as to whether or not to refer, further assess, or intervene to reduce an
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5 individual's expressed concern.
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10 **METHODS AND MATERIALS**

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12 The study was carried out from September 2005 to July 2010, with research ethics board
13 approval from participating genetics clinics: Toronto (Mount Sinai Hospital, North York General
14 Hospital, Princess Margaret Hospital); Ottawa (Children's Hospital of Eastern Ontario); and
15 Vancouver (British Columbia Cancer Agency). Individuals beginning the genetic testing process
16 for AOHD at each site were approached by genetic counsellors on the project team for their
17 permission to be contacted about the study. Those who expressed interest were mailed the
18 baseline package that included the informed consent. The informed consent included all
19 components of the study, including questionnaires, follow-up phone calls, telephone interviews,
20 as well as to the release of their genetic testing information to the research team.
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34 A two phase approach was used for this study: **Phase I: Item Generation and Refinement**,
35 and **Phase II: Validation**. The multi-stage method [24] takes validation into consideration at
36 each stage of scale development and has been used successfully in previous studies [25].
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43 **Phase I: Item Generation and Refinement.**

44 ***Item generation***

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46 To generate items for the Genetic Psychosocial Risk Instrument (GPRI), a literature search was
47 performed for the following AOHDs: Cancer (Hereditary Breast-Ovarian Cancer Syndrome/
48 Lynch Syndrome), Huntington Disease (HD), and Hemochromatosis. These diseases were
49 selected as they represented the majority of patients attending genetic clinics and had an
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3 associated available psychosocial literature for review. Databases including Cinahl (1982 to
4 2006), Medline (1966 to 2006), PsychInfo (1985 to 2006), and Pubmed (1985 to 2006) were
5 searched as well as hand search of references from major publications. Keywords included:
6 genetic screening, genetic testing, psychological, psychological well-being, psychological
7 adjustment, stress, adaptation, cancer worry, disease worry, and distress. Selection criteria for the
8 literature review included studies with a follow-up design or review articles. Each selected study
9 was reviewed by two reviewers on its quality of evidence and generalizability using a
10 standardized template. A total of 73 relevant studies were identified among the disease groups:
11 49 on cancer, 20 on HD, 2 on Hemochromatosis, and 2 described mixed conditions.
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25 Risk factors for psychological distress identified by the literature review provided the
26 basis for item generation. Items were written in a mixed format where respondents were asked
27 for their endorsement of each statement ranging from Yes/No for risk factors of binary nature, to
28 a 5-point likert-type scale for risk factors with stages in frequency and/or intensity. The
29 instrument items were further refined by 10 genetic service providers (3 geneticists, 4 genetic
30 counselors, 2 oncologists, 1 genetics nurse) rating items on *comprehension, readability, and*
31 *perceived clinical relevance* using a ten-point scale with 0 being "excellent/definitely relevant"
32 and 10 being "very poor/definitely not relevant". Risk factor items were removed if rated above
33 five by more than 3 providers. Providers were also asked to suggest additional risk factor items.
34 These suggestions were checked against the literature for empirical evidence. Following this
35 step, 7 volunteers undergoing genetic testing for AOHDs were recruited to try out the scale for
36 clarity, succinctness and relevance from the clients' perspectives. At this stage, the proposed
37 instrument consisted of 56 items: demographics (4 items); perceived risk (8 items); life events
38 and family history of the disease (8 items); perceived impact of carrying a mutation (9 items);
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3 family communication (6 items); disease specific concerns (5 items); optimism (3 items); social
4 support (3 items), pre-morbid functioning and previous psychiatric history (10 items).
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10 ***Item refinement:***

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12 Subjects: Following informed consent, a convenient sample of 141 participants who had given
13 blood for genetic tests at the Toronto and Ottawa sites completed the GPRI (using a three
14 patients per item ratio) to select the best items for the candidate scale. The participants were
15 middle aged (48.67 ± 13.29), mostly female (77%) testing for hereditary breast cancer, and many
16 (65%) had already suffered the onset of the illness.
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24 Scoring: To ensure that binary items carry an equal weight as the 5-point likert-type
25 items, a score of 5 was assigned to *Yes* and 1 to *No*. A score of 3 or mean-substitute was assigned
26 to *Not Applicable* to allow it to be counted in the total score. Reliability analysis was carried out
27 and a Cronbach's Alpha was set for .75 or higher for the scale to move to the next phase [26].
28 Any item with an item-total correlation less than .20 was identified for potential removal. Using
29 team consensus, a total of 19 items were removed, combined or substituted, resulting in a 37
30 item GPRI candidate scale at the end of phase I.
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43 **Phase II: Scale Validation**

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45 Subjects: Individuals undergoing genetic testing for one of the AOHDs in each of the five study
46 sites were invited to participate: 1) age 18 or above undergoing genetic testing for cancer, HD, or
47 Hemochromatosis; 2) fluent in English; and 3) residing within 1.5 hours driving distance from
48 study site. Although the onset of an AOHD was not an exclusion criterion, individuals in
49 advanced stages of the illness and / or who were unable to consent due to cognitive impairment
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3 were excluded. At baseline, participants were asked to complete a set of self-report
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5 questionnaires (e.g. Brief Symptom Inventory, etc.) described below within a one month period
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7 following the provision of a blood sample. For those who received a genetic test result,
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9 questionnaires were mailed within two weeks to one month of the disclosure of test result. These
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11 participants were also telephoned to complete the Hamilton Depression and Hamilton telephone-
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13 based Anxiety Scales to further assess depressive and anxiety symptoms. .
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17 Materials: At baseline, three psychosocial measures were used: GPRI Candidate Scale
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19 from Phase I. To facilitate scoring of the scale by genetic providers, scores for response to each
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21 item on the GPRI were imbedded in the questionnaire, where clinicians could calculate a total
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23 score in less than 5 minutes. Brief Symptom Inventory (BSI) The BSI is a 53-item measure of
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25 psychological distress that contains three global scales i) depression, ii) anxiety and iii)
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27 somatization [27]. While it has some limitations being a self-report measure it has been well-
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29 validated and widely used in medical and psychiatric populations to assess psychological
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31 functioning; Impact of Event Scale (IES): The IES is a 15-item, likert-style scale used to assess
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33 the experience of a specific stress response and is designed to be easily anchored in relation to a
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35 specific stressor or life event. It has been extensively utilized in the genetics literature to assess
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37 genetic testing-related distress; we similarly anchored the IES items in relation to the anticipation
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39 of the genetic test result at baseline and in relation to the actual genetic test at follow- up . The
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41 IES has two sub-scales: i) intrusive thoughts and feelings associated with the stressful life event,
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43 and ii) items associated with patterns of avoidance of certain thoughts, feelings, or situations
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53 Measures at one month post genetic testing results included: the self -reports scales of the
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55 BSI, IES and each participant received a telephone call for the telephone-based Hamilton
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3 Depression 29-item Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A). The
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5 HAM-D evaluates depressed mood, vegetative and cognitive symptoms of depression, and
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7 comorbid anxiety symptoms [29]. The HAM-A quantifies the severity of anxiety
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9 symptomatology and consists of 14 items. The HAM-D and HAM-A have demonstrated validity
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11 in clinical interview, in person or by telephone [30]. These two instruments were selected as
12
13 main outcome measures based on the literature that the standardized interview based-rating
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15 scales should be used over subjective report scales as the principal outcome criterion in
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17 psychological distress both in general practice and in research trials [34]. Cases would be defined
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19 by established cut-offs from the literature for HAM-D ≥ 12 [35] or HAM-A ≥ 10 [36]. These
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21 cut off points were established for populations in general practice, which was our study
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23 population.
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29 The one-month follow-up time point was selected as it is when elevated distress might
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31 occur [31]. In addition, the 2-week duration criterion for depression defined by the Diagnostic
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33 and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) is met by this time frame.
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39 **Assessing Psychometric Property of the Scale**

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41 As a first step, items were required to have at least an 80% response rate. Second, each item was
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43 examined to determine its contribution to the internal consistency of the total 37-item scale. The
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45 minimum item-total correlation was set at .20 [32].
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48 A principal components factor analysis with varimax rotation was performed on the
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50 candidate scale to examine the factor structure and the loading of the items. To assess the
51
52 *convergent validity* of the candidate scale, the correlations between baseline GPRI, IES and BSI
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54 were calculated. To assess the *sensitivity, specificity and predictive value* of the GPRI, the
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3 follow-up HAM-D and HAM-A were used to identify “cases” who met cut offs for either the
4 depression or anxiety symptomatology. For example, participants with a high GPRI at baseline
5 would be classified as “at risk” for future onset of adjustment difficulties. This would be
6 confirmed by a high HAM-D or HAM-A score or “case” during 1 month follow-up. Similarly,
7 those with a low GPRI score should receive low score in HAM-D or HAM-A as “non-cases”.
8 The predictive value of the GRPI, describing the number of test-positives (in our case, high
9 GPRI) who truly have the psychological condition (i.e. cases identified by HAM-D or HAM-A),
10 was tested by a Receiver Operating Characteristic (ROC) curve which visually plotted the true
11 positive rate (sensitivity) over false positive rate (1-specificity). We included cases to be
12 identified by either anxiety and/or depressive symptomatology as both have been reported in the
13 literature [8, 9].
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29 To address the issue of missing follow-up data in a cohort study, as suggested in the
30 literature [33], we tested the assumption that the sub sample with missing data had a similar
31 baseline exposure (similar GPRI) as the non-missing subsample by comparing baseline GPRI
32 between the participants and dropouts. This step assesses if there was systematic bias resulting
33 from the loss of information in the follow-up period.
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43 RESULTS

44 Participant characteristics

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46 Study packages were mailed to 1129 individuals interested in hearing more about the study. Of
47 these individuals, 722 of them consented and 712 (98%) completed the GPRI. Most participants
48 were tested for the inheritable cancers, while a small percentage of participants were tested for
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3 hemochromatosis and HD. Similar to phase I, phase II participants were mostly female, at mid-
4
5 life stage, and more than half had a past diagnosis of the disease (see table 1).
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8 **Insert Table 1 about Here**
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10 Of the 712 participants, 85 (12%) did not receive genetic testing results at the scheduled
11 follow-up time and were not eligible for follow-up measures on psychological symptoms in
12 response to a genetic testing result. Of the remaining 627 participants, 152 (24%) did not return
13 the self-administered follow-up questionnaires and 12 (2%) submitted the follow-up
14 questionnaire package but did not complete a standardized telephone interview using HAM-D
15 and HAM-A (up to 4 telephone calls were made to reach each participant). Therefore the final
16 number of participants with complete follow-up data is 463 (74%). The age, and baseline GPRI
17 score between individuals who did not receive genetic testing results (age 51.4 ± 12.7 , GPRI
18 49.3 ± 12.7), those who did not return the follow-up questionnaires (age 48.1 ± 11.6 , GPRI
19 50.2 ± 14.4) and those who completed follow-up measures (age 50.1 ± 12.8 , GPRI 49.1 ± 13.5) were
20 compared. There was no statistically significant group difference (ANOVA and all post-hoc
21 comparisons $p > 0.05$).
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38 Because of the similarity between the dropouts and completers, we proceeded with
39 reliability and validity analysis of the tool using the subsample that provided outcome data.
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42 We carried out the calculations for distress level, for example, for depression and anxiety
43 symptoms using the BSI data, for specific distress associated a genetic test result using the IES.
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45 Approximately, 13.0% to 20.1% of participants reached the threshold of moderate to severe
46 distress respectively (see table 2).
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3 HAM-D and HAM-A interview data from 463 participants were used as a further
4 validation tool to measure psychological symptoms post genetic testing results. Defined by cut-
5 offs for HAM-D ≥ 12 [35] or HAM-A ≥ 10 in the literature [36], the rates for psychological
6 distress of either depression or anxiety was 13.7% (N=63). The rate was 13% for HD, 15% for
7 breast cancer and 7% for Lynch Syndrome.
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14 15 16 17 **Reliability and Factor Analysis**

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19 A reliability analysis was performed on 37 items. Twenty items belonging to 18 questions were
20 selected based on the criteria for item selection described in the methods section. The
21 Cronbach's alpha of the 20 item GPRI was 0.81 suggesting a good level of internal consistency.
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27 The factor analysis resulted in a psychometrically sound 3-factor solution, with subscales
28 representing the dimensions of: 1) *Perceived impact and personal adjustment to genetic testing*
29 (12 items); 2) *Past history of mental health concerns* (5 items) and 3) *Personal history/family*
30 *history/loss to cancer* (3 items). All three factors met the minimum Eigenvalue criteria of 1.
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36 The first, 12-item factor (ALPHA = 0.85), accounting for 22% of the variance, includes
37 items associated with the anticipated or experienced impact of being at high risk for AOHD.
38 Example items included: "My worries about the disease affect my daily mood"; "The disease for
39 which I am at risk is currently causing a significant disruption in my family life".
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46 The second 5-item factor (ALPHA = 0.76), accounted for an additional 14% of the total
47 variance, and reflected a sense of a person's past history or vulnerability in the area of mental
48 health, e.g. "I have had emotional problems in the past", These items have been used in other
49 medical health areas [37, 38] and tend to be predictive of maladjustment [20] following a life
50 event.
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3 The third 3 item factor (ALPHA = 0.08), accounted for 8% of the total variance and
4 pertained to personal or family-related experiences associated with the hereditary disorder for
5 which the participant is undergoing testing. . Examples include: “I have a personal diagnosis of
6 the disease for which I am receiving counseling”; “I lost a close family member to the disease for
7 which I am receiving counseling”; and “I have taken care of a very ill parent or another close
8 family member”. These 3 final items had low item total correlation because they were different
9 from the rest of the items in that they focused on direct experiences related to the illness, rather
10 than psychosocial-related items. These items were kept in the scale as they contributed
11 significantly to the overall variance, and correlated highly with HAM-D and HAM-A. To
12 determine the relationships between the three factors/subscales, correlations were computed.
13 Factor1 and factor2 had moderate correlations with each other (factor1/factor2 $r=0.30$, $p<0.01$).
14 The correlation of the first two factors with factor3 was much lower as expected (factor1/factor3
15 $r=0.06$, and factor2/factor3 $r=0.01$, not statistically significant). These results support the
16 multidimensional character of the GPRI scale (see Table 3).
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37 **Insert Table 3 about Here**
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39 One additional statement “I am interested in talking to a counselor about one or more of
40 these concerns” was added to the tool at the end as suggested by participants and providers to
41 remind them the option of seeing a counselor if required. This statement is not part of the items
42 examined during the instrument development and therefore does not carry a score.
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48 The total score for the 20 item GPRI ranged from 20 to 100, with a sample mean
49 49.36 ± 13.23 . The total was calculated by the sum of the raw scores for each of the statements.
50 Females had a significantly higher score for the GPRI than males (50.37 ± 13.14 vs. 41.91 ± 11.47 ,
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3 p<0.01), and participants testing for HD had a higher, but non-significant score than participants
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5 testing for cancer (52.24±13.24 vs. 49.37±13.22, n.s.).
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8 9 **Validity**

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11 Construct validity – correlations: The GPRI was assessed for its correlation with other
12
13 standardized self-report measures of psychological functioning collected at baseline. Convergent
14
15 validity was demonstrated by the correlation between the GPRI and the following measures: a
16
17 positive correlation with the IES total score at $r = .51$, $p < .001$, and with BSI at $r = .58$, $p < .001$.
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21 Sensitivity, specificity and the predictive value of GPRI for future distress: The telephone
22
23 interview-based HAM-D and HAM-A were used to identify subjects who presented specific
24
25 psychological symptoms of distress such as depression and/or anxiety during the one month post
26
27 genetic testing follow-up. A total of 63 “cases” (13.6% of 463 completers) were identified as
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29 having psychological distress levels above specified thresholds defined in the methods section
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31 for either anxiety or depression symptoms or both. About 23% among participants testing
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33 positive met the distress threshold, as did 10% among those with negative results, and 20%
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35 among uninformative. Participants scoring above HAM-D (N=55) threshold had significantly
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37 higher GPRI scores than participants below the threshold (N=408) (61.12±13.27 vs.
38
39 47.91±12.27, $p < 0.01$). Same patterns were observed for HAM-A high (N=40) vs. low (N=423)
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41 (62.53±12.92 vs. 48.25± 12.43, $p < 0.01$).
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48 Other demographic characteristics of these 63 subjects include: most were female and
49
50 undergoing testing for BRCA1/2, which was similar to the whole sample of 712 (table 1).

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52 Compared with the whole sample, these subjects had a slightly higher percentage of personal
53
54 history of cancer (65% vs. 62%), higher rate of recent significant event of loss (56% vs. 47%),
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56 greater percentage reporting disease worries affecting mood (54.8% vs. 27%), having a feeling of
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3 sadness in the past month (46% vs. 17%) and anxiousness in the past month (33% vs. 17%). Our
4 instrument captured all of these characteristics of this subsample.
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8 The predictive value of a test describes how many of the test-positives (in this case, a
9 high score on GPRI) truly have the psychological condition. An ROC curve was used to plot the
10 true positive rate (sensitivity) over the false positive rate (1-specificity). A good ROC curve rises
11 sharply, indicating a high proportion in true positive and a low proportion of false positives. The
12 ROC curve for the GPRI was 0.78, which is considered as an indicator of an adequate screening
13 instrument [39].
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22 An important purpose of the GRPI in our study was to identify individuals at risk for post
23 genetic testing psychological distress. Therefore, the cutoff value was set to maximize sensitivity
24 – in another word, not to miss detecting a “case”. Using a GPRI cut off score of 50, the
25 instrument was able to predict 84% of the “cases” identified by HAM-D or HAM-A conducted
26 post genetic testing results, with a specificity value of 60% (Figure 1).
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38 **DISCUSSION**

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40 The aim of this study was to develop a brief, easy-to-use psychosocial screening instrument
41 specific for the genetic testing context and to examine its reliability and validity (Appendix A).
42
43 To our knowledge this is the first report of a psychosocial screening instrument for use across
44 AOHD. Unlike current psychological instruments used mainly in research studies in genetics
45 clinics to identify existing global symptoms of depression and anxiety, or impacts, the GPRI
46 assesses *psychological risk factors*, such as the specific anticipated impacts of a genetic testing
47 result and the perception of the disease. The GPRI demonstrates promising psychometric
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3 properties as a tool designed to assist genetics health care providers determine which of their
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5 patients undergoing genetic testing for AOHD is at increased psychological risk and should
6
7 likely be considered for additional psychosocial support to facilitate adjustment to a test result.
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10 A high reliability was demonstrated by a Cronbach's Alpha at 0.81, moderate to high
11
12 item-total correlation and inter-item correlation of the whole scale. The construct validity of the
13
14 scale was supported by high correlations between the GPRI and standardized psychological
15
16 measures (BSI, IES). The clinical utility and predictive value of the GPRI was supported as
17
18 well. A GPRI score above the cutoff of 50 at baseline was able to predict 84% of “distress” cases
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20 identified by HAM-D or HAM-A, a strong indicator of its potential usefulness in a clinical
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22 setting.
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27 A brief self-administered screening tool will be easy and likely highly acceptable for
28
29 incorporation into genetics clinics. The GPRI can be completed and scored quickly during
30
31 clinical visits and without additional burden to patients and health providers. In addition, by
32
33 focusing specifically on known risk factors associated with inheritable illness, the instrument
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35 will be perceived as being more clinically relevant and acceptable to patients. Patients with
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37 higher GPRI scores can be flagged and either receive telephone follow-up to further assess
38
39 concerns or potential distress or be invited back for an appointment for further assessment and
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41 required psychological treatment.
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46 Alternatively, genetic clinics with available psychosocial personnel could utilize the tool
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48 to guide referrals for a formal psychosocial assessment that can further explore and address
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50 specific self-reported psychological factors. For example, in the case where an individual is
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52 particularly fearful of developing an illness or is concerned about specific impacts, such as
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54 expecting relationship or family communications difficulties, information on communication
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3 strategies, personal coaching or family-based interventions could be employed to support the
4 individual. For an individuals who reports a past history of psychological illness, a mental health
5 professional could further assess current psychological functioning and implement specific
6 approaches, and could offer cognitive-behavioral strategies or psychotropic medication to assist
7 in the management of anxiety or depressive symptoms [40]. Several items incorporate variables
8 related to heritable disease experiences and associated perceptions which can be used to guide
9 educational interventions to correct any myths or beliefs.

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20 The scale appeared highly acceptable to patients. A high face validity will contribute to
21 better scale uptake being perceived as “user friendly” and clinically relevant, compared for
22 example, to a standardized psychological instrument on depression, which have demonstrated
23 some barriers to clinic uptake [19]. The GPRI in contrast might be considered as a
24 “communimetric measure”, that is, the items themselves are useful for the clinician in
25 communicating concerns about specific areas of functioning directly with the patient [41].
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34 Left untreated, significant levels of psychological symptoms may lead to lower quality
35 of life [40], and lower satisfaction with genetics services [21]. A psychological screening
36 approach allows both for careful monitoring during a known stressful period-that of awaiting test
37 results [42], and provides an opportunity for any planned follow-up care. Flagging those
38 individuals who might benefit most from psychosocial care also best utilizes the often limited
39 psychological resources in genetic clinics [2, 20, 21].
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48 Our study findings are limited by the characteristics of the sample, in that most
49 participants were female and undergoing testing for *BRCA1/2*. This pattern is similar to that
50 observed in the literature on genetic testing for AOHD, which is predominantly focused on
51 Hereditary Breast-Ovarian Cancer Syndrome. We attempted to obtain a larger sample of
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3 individuals undergoing genetic testing for HD or Lynch Syndrome which would presumably
4 provide a greater sample of males. However, these sample pools were much smaller. However,
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6 this study and the resulting GPRI represent an attempt to begin the development of a general tool
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8 that addresses concerns that are relevant across genetic samples. Our belief stemming from
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10 clinical practice and the associated literature suggest that the identified mental health issues or
11
12 adjustment risk factors are not disease specific. We suggest that future studies further address the
13
14 validity of GPRI in male populations and in the rare adult onset hereditary diseases, such as HD.
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16 Future studies should also include randomized controlled trials to assess the effectiveness of the
17
18 GPRI in predicting distress, its impact on referral patterns, patient and provider satisfaction, as
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20 well as on cost-effectiveness. The GPRI could also be evaluated in primary care settings where
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22 genetics services might be offered more frequently to meet the demand.
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32 CONCLUSIONS

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34 This is the first study to develop a screening tool specifically to help identify individuals
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36 undergoing genetic testing for AOHD who are at increased psychological risk. The study
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38 resulted in an easy to use, 20-item scale consisting of 3 factors with promising psychometric
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40 properties. The GPRI has the potential to be used as a clinical screening tool and as a validated
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42 measure for future studies. Future work can examine its impact on clinical referral patterns
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44 within the field of genetics, and on its acceptability, reliability and validity with larger samples
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46 of individuals undergoing genetic testing for HD, Lynch Syndrome, and potentially for emerging
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48 new genetic tests, such as for cardiac or psychiatric disorders.
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Data Sharing Statement: There is no additional data available

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

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Contributorship Statements

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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.

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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.

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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.

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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.

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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.

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Title

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

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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 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.

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3 instruments measuring breast/ovarian cancer worry) have demonstrated higher prevalence levels
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6 [6, 7].
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8 The risk factors for psychological symptoms amongst individuals undergoing genetic
9 testing have been delineated in several studies [4, 8, 9]. While there is generally elevated
10 distress using global measures for depression or anxiety among those who receive positive test
11 results [9-11], individuals testing negative or receiving uninformative results may also have
12 adjustment difficulties [12] following testing. For example, individuals may feel guilt or
13 continue to worry about their disease risk even when testing negative [2, 7, 12]. These findings
14 highlight the importance of considering risk factors in addition to the type of test result itself.
15 Individuals who have elevated psychological symptoms at the pre-test stage and those with a
16 previous psychiatric history (i.e., depression) are particularly at risk for an adverse psychological
17 outcome after testing [2, 8, 9].
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32 Additional risk factors for distress are more specific to the genetics context and include
33 the level of penetrance of the gene mutation or degree of certainty of developing the disease [4].
34 The perception of control over the disease (including the number of prevention/treatment
35 options) and perception of the immediacy of risk (proximity in age to perceived disease onset)
36 are important predictors [4, 13]. The expectation of a negative test result can play a role in
37 adjustment, as can the context of test results of other family members [9, 14]. As in other
38 medical areas, specific coping styles can affect adjustment [15]. The prior experiences with loss
39 of family members to disease, as well as the developmental level (i.e. young age) of the
40 individual at the time of the loss [2, 3, 16] are significant factors affecting potential adjustment.
41 In addition, the prior experience of giving care to a family member with the disease and lower
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3 levels of social support have been associated with poorer adjustment following a positive test
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5 result [2-4, 8, 16].
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8 It is clear that there is not one predominant factor, but rather, a series of variables that can
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10 be assessed prior to receiving a test result that may contribute to elevated levels of psychological
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12 distress following genetic testing [2, 17]. Emotional reactions may impede the assimilation of
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14 risk information and the adoption of preventive measures recommended following notification of
15
16 a mutation [2, 18]. Psychological distress occurs along a continuum [19, 20] and can be difficult
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18 to identify by health professionals [21]. Distress may not become manifest to the health care
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20 team until the patient reaches an observable crisis level, i.e. the onset of severe depression or
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22 anxiety, or significant conflicts with the family. An early screening instrument would enable
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24 healthcare providers to identify patients being at higher psychological risk in order that
25
26 appropriate support can be given at the right time. In fact, there is now a general consensus that
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28 genetic testing should be accompanied by psychological support to promote optimal adjustment
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30 [2, 22].
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39 **Screening for Psychological Risk Factors- Why is it necessary?**

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41 The gold standard for identifying psychologically distressed individuals involves structured
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43 clinical interviews administered by a clinical psychologist or psychiatrist [21]. However, it is too
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45 costly and often not feasible in genetic clinics. Standardized measures of psychological
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47 functioning (e.g. global scales of depression or anxiety) can also be used as a method for
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49 identifying distress. However, few clinics use these measures in practice because of personnel
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51 and time requirements for scoring and interpretation of them. Furthermore, items on these
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53 measures typically focus on symptoms of anxiety or depression, rather than on variables
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3 associated with heritable disease or genetic testing or risk, which may pose barriers for use by
4 genetics health service providers who may prefer instruments that, at face value, appear to them
5 and their patients as being clinically more relevant to the genetic testing context.
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10 More recently, new outcome measures designed to assess the psychological impact of
11 receiving genetic information have been developed. For example, the Multidimensional Impact
12 of Cancer Risk Assessment (MICRA) is designed to assess concerns and impacts associated with
13 genetic testing for BRCA1/2 [19] and another tool, the Psychological Adaptation to Genetic
14 Information Scale, is now available [23]. While these measures will require further validation
15 they provide more clinically relevant approaches to capturing specific impacts of genetic
16 information, such as the increased sense of vulnerability often experienced following genetic
17 testing [19, 23].
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29 Measures of global psychological functioning and the evolving outcome measurement
30 tools for the genetics field are not designed to “predict” vulnerability for future distress, but
31 rather, measure current distress levels. Screening, the aim of the tool developed in this study in
32 contrast, is a rapid, cost-effective alternative [21] to prospectively identify individuals who may
33 experience significant difficulty in their attempts to adapt to their genetic information [17]. A
34 screening tool enables providers to offer timely and focused educational and psychosocial
35 interventions to *prevent* future distress.
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46 The primary *objective* of this study was to develop a brief, reliable and valid
47 psychological risk screening instrument for use in the genetic testing context. The new
48 instrument aimed to incorporate empirically based risk factors for psychological symptoms and
49 would need to show a high sensitivity, specificity and predictive validity indicating risk for
50 future distress post genetic testing results. A cutoff point would need to be determined to guide
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3 clinical decisions as to whether or not to refer, further assess, or intervene to reduce an
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5 individual's expressed concern.
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10 **METHODS AND MATERIALS**

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12 The study was carried out from September 2005 to July 2010, with research ethics board
13 approval from participating genetics clinics: Toronto (Mount Sinai Hospital, North York General
14 Hospital, Princess Margaret Hospital); Ottawa (Children's Hospital of Eastern Ontario); and
15 Vancouver (British Columbia Cancer Agency). Individuals beginning the genetic testing process
16 for AOHD at each site were approached by genetic counsellors on the project team for their
17 permission to be contacted about the study. Those who expressed interest were mailed the
18 baseline package that included the informed consent. The informed consent included all
19 components of the study, including questionnaires, follow-up phone calls, telephone interviews,
20 as well as to the release of their genetic testing information to the research team.
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34 A two phase approach was used for this study: **Phase I: Item Generation and Refinement**,
35 and **Phase II: Validation**. The multi-stage method [24] takes validation into consideration at
36 each stage of scale development and has been used successfully in previous studies [25].
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43 **Phase I: Item Generation and Refinement.**

44 ***Item generation***

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46 To generate items for the Genetic Psychosocial Risk Instrument (GPRI), a literature search was
47 performed for the following AOHDs: Cancer (Hereditary Breast-Ovarian Cancer Syndrome/
48 Lynch Syndrome), Huntington Disease (HD), and Hemochromatosis. These diseases were
49 selected as they represented the majority of patients attending genetic clinics and had an
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3 associated available psychosocial literature for review. Databases including Cinahl (1982 to
4 2006), Medline (1966 to 2006), PsychInfo (1985 to 2006), and Pubmed (1985 to 2006) were
5 searched as well as hand search of references from major publications. Keywords included:
6 genetic screening, genetic testing, psychological, psychological well-being, psychological
7 adjustment, stress, adaptation, cancer worry, disease worry, and distress. Selection criteria for the
8 literature review included studies with a follow-up design or review articles. Each selected study
9 was reviewed by two reviewers on its quality of evidence and generalizability using a
10 standardized template. A total of 73 relevant studies were identified among the disease groups:
11 49 on cancer, 20 on HD, 2 on Hemochromatosis, and 2 described mixed conditions.
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25 Risk factors for psychological distress identified by the literature review provided the
26 basis for item generation. Items were written in a mixed format where respondents were asked
27 for their endorsement of each statement ranging from Yes/No for risk factors of binary nature, to
28 a 5-point likert-type scale for risk factors with stages in frequency and/or intensity. The
29 instrument items were further refined by 10 genetic service providers (3 geneticists, 4 genetic
30 counselors, 2 oncologists, 1 genetics nurse) rating items on *comprehension, readability, and*
31 *perceived clinical relevance* using a ten-point scale with 0 being "excellent/definitely relevant"
32 and 10 being "very poor/definitely not relevant". Risk factor items were removed if rated above
33 five by more than 3 providers. Providers were also asked to suggest additional risk factor items.
34 These suggestions were checked against the literature for empirical evidence. Following this
35 step, 7 volunteers undergoing genetic testing for AOHDs were recruited to try out the scale for
36 clarity, succinctness and relevance from the clients' perspectives. At this stage, the proposed
37 instrument consisted of 56 items: demographics (4 items); perceived risk (8 items); life events
38 and family history of the disease (8 items); perceived impact of carrying a mutation (9 items);
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3 family communication (6 items); disease specific concerns (5 items); optimism (3 items); social
4 support (3 items), pre-morbid functioning and previous psychiatric history (10 items).
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10 ***Item refinement:***

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12 Subjects: Following informed consent, a convenient sample of 141 participants who had given
13 blood for genetic tests at the Toronto and Ottawa sites completed the GPRI (using a three
14 patients per item ratio) to select the best items for the candidate scale. The participants were
15 middle aged (48.67 ± 13.29), mostly female (77%) testing for hereditary breast cancer, and many
16 (65%) had already suffered the onset of the illness.
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24 Scoring: To ensure that binary items carry an equal weight as the 5-point likert-type
25 items, a score of 5 was assigned to *Yes* and 1 to *No*. A score of 3 or mean-substitute was assigned
26 to *Not Applicable* to allow it to be counted in the total score. Reliability analysis was carried out
27 and a Cronbach's Alpha was set for .75 or higher for the scale to move to the next phase [26].
28 Any item with an item-total correlation less than .20 was identified for potential removal. Using
29 team consensus, a total of 19 items were removed, combined or substituted, resulting in a 37
30 item GPRI candidate scale at the end of phase I.
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43 **Phase II: Scale Validation**

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45 Subjects: Individuals undergoing genetic testing for one of the AOHDs in each of the five study
46 sites were invited to participate: 1) age 18 or above undergoing genetic testing for cancer, HD, or
47 Hemochromatosis; 2) fluent in English; and 3) residing within 1.5 hours driving distance from
48 study site. Although the onset of an AOHD was not an exclusion criterion, individuals in
49 advanced stages of the illness and / or who were unable to consent due to cognitive impairment
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3 were excluded. At baseline, participants were asked to complete a set of self-report
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5 questionnaires (e.g. Brief Symptom Inventory, etc.) described below within a one month period
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7 following the provision of a blood sample. For those who received a genetic test result,
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9 questionnaires were mailed within two weeks to one month of the disclosure of test result. These
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11 participants were also telephoned to complete the Hamilton Depression and Hamilton telephone-
12
13 based Anxiety Scales to further assess depressive and anxiety symptoms. .
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17 Materials: At baseline, three psychosocial measures were used: GPRI Candidate Scale
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19 from Phase I. To facilitate scoring of the scale by genetic providers, scores for response to each
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21 item on the GPRI were imbedded in the questionnaire, where clinicians could calculate a total
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23 score in less than 5 minutes. Brief Symptom Inventory (BSI) The BSI is a 53-item measure of
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25 psychological distress that contains three global scales i) depression, ii) anxiety and iii)
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27 somatization [27]. While it has some limitations being a self-report measure it has been well-
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29 validated and widely used in medical and psychiatric populations to assess psychological
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31 functioning; Impact of Event Scale (IES): The IES is a 15-item, likert-style scale used to assess
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33 the experience of a specific stress response and is designed to be easily anchored in relation to a
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35 specific stressor or life event. It has been extensively utilized in the genetics literature to assess
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37 genetic testing-related distress; we similarly anchored the IES items in relation to the anticipation
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39 of the genetic test result at baseline and in relation to the actual genetic test at follow- up . The
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41 IES has two sub-scales: i) intrusive thoughts and feelings associated with the stressful life event,
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43 and ii) items associated with patterns of avoidance of certain thoughts, feelings, or situations
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53 Measures at one month post genetic testing results included: the self -reports scales of the
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55 BSI, IES and each participant received a telephone call for the telephone-based Hamilton
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3 Depression 29-item Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A). The
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5 HAM-D evaluates depressed mood, vegetative and cognitive symptoms of depression, and
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7 comorbid anxiety symptoms [29]. The HAM-A quantifies the severity of anxiety
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9 symptomatology and consists of 14 items. The HAM-D and HAM-A have demonstrated validity
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11 in clinical interview, in person or by telephone [30]. These two instruments were selected as
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13 main outcome measures based on the literature that the standardized interview based-rating
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15 scales should be used over subjective report scales as the principal outcome criterion in
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17 psychological distress both in general practice and in research trials [34]. Cases would be defined
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19 by established cut-offs from the literature for HAM-D ≥ 12 [35] or HAM-A ≥ 10 [36]. These
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21 cut off points were established for populations in general practice, which was our study
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23 population.
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29 The one-month follow-up time point was selected as it is when elevated distress might
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31 occur [31]. In addition, the 2-week duration criterion for depression defined by the Diagnostic
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33 and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) is met by this time frame.
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39 **Assessing Psychometric Property of the Scale**

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41 As a first step, items were required to have at least an 80% response rate. Second, each item was
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43 examined to determine its contribution to the internal consistency of the total 37-item scale. The
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45 minimum item-total correlation was set at .20 [32].
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48 A principal components factor analysis with varimax rotation was performed on the
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50 candidate scale to examine the factor structure and the loading of the items. To assess the
51
52 *convergent validity* of the candidate scale, the correlations between baseline GPRI, IES and BSI
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54 were calculated. To assess the *sensitivity, specificity and predictive value* of the GPRI, the
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3 follow-up HAM-D and HAM-A were used to identify “cases” who met cut offs for either the
4 depression or anxiety symptomatology. For example, participants with a high GPRI at baseline
5 would be classified as “at risk” for future onset of adjustment difficulties. This would be
6 confirmed by a high HAM-D or HAM-A score or “case” during 1 month follow-up. Similarly,
7 those with a low GPRI score should receive low score in HAM-D or HAM-A as “non-cases”.
8 The predictive value of the GRPI, describing the number of test-positives (in our case, high
9 GPRI) who truly have the psychological condition (i.e. cases identified by HAM-D or HAM-A),
10 was tested by a Receiver Operating Characteristic (ROC) curve which visually plotted the true
11 positive rate (sensitivity) over false positive rate (1-specificity). We included cases to be
12 identified by either anxiety and/or depressive symptomatology as both have been reported in the
13 literature [8, 9].
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29 To address the issue of missing follow-up data in a cohort study, as suggested in the
30 literature [33], we tested the assumption that the sub sample with missing data had a similar
31 baseline exposure (similar GPRI) as the non-missing subsample by comparing baseline GPRI
32 between the participants and dropouts. This step assesses if there was systematic bias resulting
33 from the loss of information in the follow-up period.
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43 RESULTS

44 Participant characteristics

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46 Study packages were mailed to 1129 individuals interested in hearing more about the study. Of
47 these individuals, 722 of them consented and 712 (98%) completed the GPRI. Most participants
48 were tested for the inheritable cancers, while a small percentage of participants were tested for
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3 hemochromatosis and HD. Similar to phase I, phase II participants were mostly female, at mid-
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5 life stage, and more than half had a past diagnosis of the disease (see table 1).
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8 **Insert Table 1 about Here**
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10 Of the 712 participants, 85 (12%) did not receive genetic testing results at the scheduled
11 follow-up time and were not eligible for follow-up measures on psychological symptoms in
12 response to a genetic testing result. Of the remaining 627 participants, 152 (24%) did not return
13 the self-administered follow-up questionnaires and 12 (2%) submitted the follow-up
14 questionnaire package but did not complete a standardized telephone interview using HAM-D
15 and HAM-A (up to 4 telephone calls were made to reach each participant). Therefore the final
16 number of participants with complete follow-up data is 463 (74%). The age, and baseline GPRI
17 score between individuals who did not receive genetic testing results (age 51.4 ± 12.7 , GPRI
18 49.3 ± 12.7), those who did not return the follow-up questionnaires (age 48.1 ± 11.6 , GPRI
19 50.2 ± 14.4) and those who completed follow-up measures (age 50.1 ± 12.8 , GPRI 49.1 ± 13.5) were
20 compared. There was no statistically significant group difference (ANOVA and all post-hoc
21 comparisons $p > 0.05$).
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38 Because of the similarity between the dropouts and completers, we proceeded with
39 reliability and validity analysis of the tool using the subsample that provided outcome data.
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42 We carried out the calculations for distress level, for example, for depression and anxiety
43 symptoms using the BSI data, for specific distress associated a genetic test result using the IES.
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45 Approximately, 13.0% to 20.1% of participants reached the threshold of moderate to severe
46 distress respectively (see table 2).
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3 HAM-D and HAM-A interview data from 463 participants were used as a further
4 validation tool to measure psychological symptoms post genetic testing results. Defined by cut-
5 offs for HAM-D ≥ 12 [35] or HAM-A ≥ 10 in the literature [36], the rates for psychological
6 distress of either depression or anxiety was 13.7% (N=63). The rate was 13% for HD, 15% for
7 breast cancer and 7% for Lynch Syndrome.
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14 15 16 17 **Reliability and Factor Analysis**

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19 A reliability analysis was performed on 37 items. Twenty items belonging to 18 questions were
20 selected based on the criteria for item selection described in the methods section. The
21 Cronbach's alpha of the 20 item GPRI was 0.81 suggesting a good level of internal consistency.
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27 The factor analysis resulted in a psychometrically sound 3-factor solution, with subscales
28 representing the dimensions of: 1) *Perceived impact and personal adjustment to genetic testing*
29 (12 items); 2) *Past history of mental health concerns* (5 items) and 3) *Personal history/family*
30 *history/loss to cancer* (3 items). All three factors met the minimum Eigenvalue criteria of 1.
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36 The first, 12-item factor (ALPHA = 0.85), accounting for 22% of the variance, includes
37 items associated with the anticipated or experienced impact of being at high risk for AOHD.
38 Example items included: "My worries about the disease affect my daily mood"; "The disease for
39 which I am at risk is currently causing a significant disruption in my family life".
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46 The second 5-item factor (ALPHA = 0.76), accounted for an additional 14% of the total
47 variance, and reflected a sense of a person's past history or vulnerability in the area of mental
48 health, e.g. "I have had emotional problems in the past". These items have been used in other
49 medical health areas [37, 38] and tend to be predictive of maladjustment [20] following a life
50 event.
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3 The third 3 item factor (ALPHA = 0.08), accounted for 8% of the total variance and
4 pertained to personal or family-related experiences associated with the heritable disorder for
5 which the participant is undergoing testing. . Examples include: “I have a personal diagnosis of
6 the disease for which I am receiving counseling”; “I lost a close family member to the disease for
7 which I am receiving counseling”; and “I have taken care of a very ill parent or another close
8 family member”. These 3 final items had low item total correlation because they were different
9 from the rest of the items in that they focused on direct experiences related to the illness, rather
10 than psychosocial-related items. These items were kept in the scale as they contributed
11 significantly to the overall variance, and correlated highly with HAM-D and HAM-A. To
12 determine the relationships between the three factors/subscales, correlations were computed.
13 Factor1 and factor2 had moderate correlations with each other (factor1/factor2 $r=0.30$, $p<0.01$).
14 The correlation of the first two factors with factor3 was much lower as expected (factor1/factor3
15 $r=0.06$, and factor2/factor3 $r=0.01$, not statistically significant). These results support the
16 multidimensional character of the GPRI scale (see Table 3).
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36 **Insert Table 3 about Here**
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38 One additional statement “I am interested in talking to a counselor about one or more of
39 these concerns” was added to the tool at the end as suggested by participants and providers to
40 remind them the option of seeing a counselor if required. This statement is not part of the items
41 examined during the instrument development and therefore does not carry a score.
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48 The total score for the 20 item GPRI ranged from 20 to 100, with a sample mean
49 49.36 ± 13.23 . The total was calculated by the sum of the raw scores for each of the statements.
50 Females had a significantly higher score for the GPRI than males (50.37 ± 13.14 vs. 41.91 ± 11.47 ,
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3 p<0.01), and participants testing for HD had a higher, but non-significant score than participants
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5 testing for cancer (52.24±13.24 vs. 49.37±13.22, n.s.).
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8 9 **Validity**

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11 Construct validity – correlations: The GPRI was assessed for its correlation with other
12
13 standardized self-report measures of psychological functioning collected at baseline. Convergent
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15 validity was demonstrated by the correlation between the GPRI and the following measures: a
16
17 positive correlation with the IES total score at $r = .51$, $p < .001$, and with BSI at $r = .58$, $p < .001$.
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21 Sensitivity, specificity and the predictive value of GPRI for future distress: The telephone
22
23 interview-based HAM-D and HAM-A were used to identify subjects who presented specific
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25 psychological symptoms of distress such as depression and/or anxiety during the one month post
26
27 genetic testing follow-up. A total of 63 “cases” (13.6% of 463 completers) were identified as
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29 having psychological distress levels above specified thresholds defined in the methods section
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31 for either anxiety or depression symptoms or both. About 23% among participants testing
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33 positive met the distress threshold, as did 10% among those with negative results, and 20%
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35 among uninformative. Participants scoring above HAM-D (N=55) threshold had significantly
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37 higher GPRI scores than participants below the threshold (N=408) (61.12±13.27 vs.
38
39 47.91±12.27, $p < 0.01$). Same patterns were observed for HAM-A high (N=40) vs. low (N=423)
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41 (62.53±12.92 vs. 48.25± 12.43, $p < 0.01$).
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48 Other demographic characteristics of these 63 subjects include: most were female and
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50 undergoing testing for BRCA1/2, which was similar to the whole sample of 712 (table 1).
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52 Compared with the whole sample, these subjects had a slightly higher percentage of personal
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54 history of cancer (65% vs. 62%), higher rate of recent significant event of loss (56% vs. 47%),
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56 greater percentage reporting disease worries affecting mood (54.8% vs. 27%), having a feeling of
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3 sadness in the past month (46% vs. 17%) and anxiousness in the past month (33% vs. 17%). Our
4 instrument captured all of these characteristics of this subsample.
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8 The predictive value of a test describes how many of the test-positives (in this case, a
9 high score on GPRI) truly have the psychological condition. An ROC curve was used to plot the
10 true positive rate (sensitivity) over the false positive rate (1-specificity). A good ROC curve rises
11 sharply, indicating a high proportion in true positive and a low proportion of false positives. The
12 ROC curve for the GPRI was 0.78, which is considered as an indicator of an adequate screening
13 instrument [39].
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22 An important purpose of the GRPI in our study was to identify individuals at risk for post
23 genetic testing psychological distress. Therefore, the cutoff value was set to maximize sensitivity
24 – in another word, not to miss detecting a “case”. Using a GPRI cut off score of 50, the
25 instrument was able to predict 84% of the “cases” identified by HAM-D or HAM-A conducted
26 post genetic testing results, with a specificity value of 60% (Figure 1).
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39 **DISCUSSION**

40 The aim of this study was to develop a brief, easy-to-use psychosocial screening instrument
41 specific for the genetic testing context and to examine its reliability and validity (Appendix A).
42 To our knowledge this is the first report of a psychosocial screening instrument for use across
43 AOHD. Unlike current psychological instruments used mainly in research studies in genetics
44 clinics to identify existing global symptoms of depression and anxiety, or impacts, the GPRI
45 assesses *psychological risk factors*, such as the specific anticipated impacts of a genetic testing
46 result and the perception of the disease. The GPRI demonstrates promising psychometric
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3 properties as a tool designed to assist genetics health care providers determine which of their
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5 patients undergoing genetic testing for AOHD is at increased psychological risk and should
6
7 likely be considered for additional psychosocial support to facilitate adjustment to a test result.
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10 A high reliability was demonstrated by a Cronbach's Alpha at 0.81, moderate to high
11
12 item-total correlation and inter-item correlation of the whole scale. The construct validity of the
13
14 scale was supported by high correlations between the GPRI and standardized psychological
15
16 measures (BSI, IES). The clinical utility and predictive value of the GPRI was supported as
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18 well. A GPRI score above the cutoff of 50 at baseline was able to predict 84% of “distress” cases
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20 identified by HAM-D or HAM-A, a strong indicator of its potential usefulness in a clinical
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22 setting.
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27 A brief self-administered screening tool will be easy and likely highly acceptable for
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29 incorporation into genetics clinics. The GPRI can be completed and scored quickly during
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31 clinical visits and without additional burden to patients and health providers. In addition, by
32
33 focusing specifically on known risk factors associated with inheritable illness, the instrument
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35 will be perceived as being more clinically relevant and acceptable to patients. Patients with
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37 higher GPRI scores can be flagged and either receive telephone follow-up to further assess
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39 concerns or potential distress or be invited back for an appointment for further assessment and
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41 required psychological treatment.
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46 Alternatively, genetic clinics with available psychosocial personnel could utilize the tool
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48 to guide referrals for a formal psychosocial assessment that can further explore and address
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50 specific self-reported psychological factors. For example, in the case where an individual is
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52 particularly fearful of developing an illness or is concerned about specific impacts, such as
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54 expecting relationship or family communications difficulties, information on communication
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3 strategies, personal coaching or family-based interventions could be employed to support the
4 individual. For an individuals who reports a past history of psychological illness, a mental health
5 professional could further assess current psychological functioning and implement specific
6 approaches, and could offer cognitive-behavioral strategies or psychotropic medication to assist
7 in the management of anxiety or depressive symptoms [40]. Several items incorporate variables
8 related to heritable disease experiences and associated perceptions which can be used to guide
9 educational interventions to correct any myths or beliefs.

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

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3 individuals undergoing genetic testing for HD or Lynch Syndrome which would presumably
4 provide a greater sample of males. However, these sample pools were much smaller. However,
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6 this study and the resulting GPRI represent an attempt to begin the development of a general tool
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8 that addresses concerns that are relevant across genetic samples. Our belief stemming from
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10 clinical practice and the associated literature suggest that the identified mental health issues or
11
12 adjustment risk factors are not disease specific. We suggest that future studies further address the
13
14 validity of GPRI in male populations and in the rare adult onset hereditary diseases, such as HD.
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16 Future studies should also include randomized controlled trials to assess the effectiveness of the
17
18 GPRI in predicting distress, its impact on referral patterns, patient and provider satisfaction, as
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20 well as on cost-effectiveness. The GPRI could also be evaluated in primary care settings where
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22 genetics services might be offered more frequently to meet the demand.
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32 CONCLUSIONS

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

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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.

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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	85 (12%)
	Female	627 (88%)
Type of AOHD being tested: n (%)	Cancer (BRCA)	580 (82%)
	Cancer (other, ie, Colon)	90 (13%)
	Huntington disease	31 (4%)
	Hemochromatosis	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

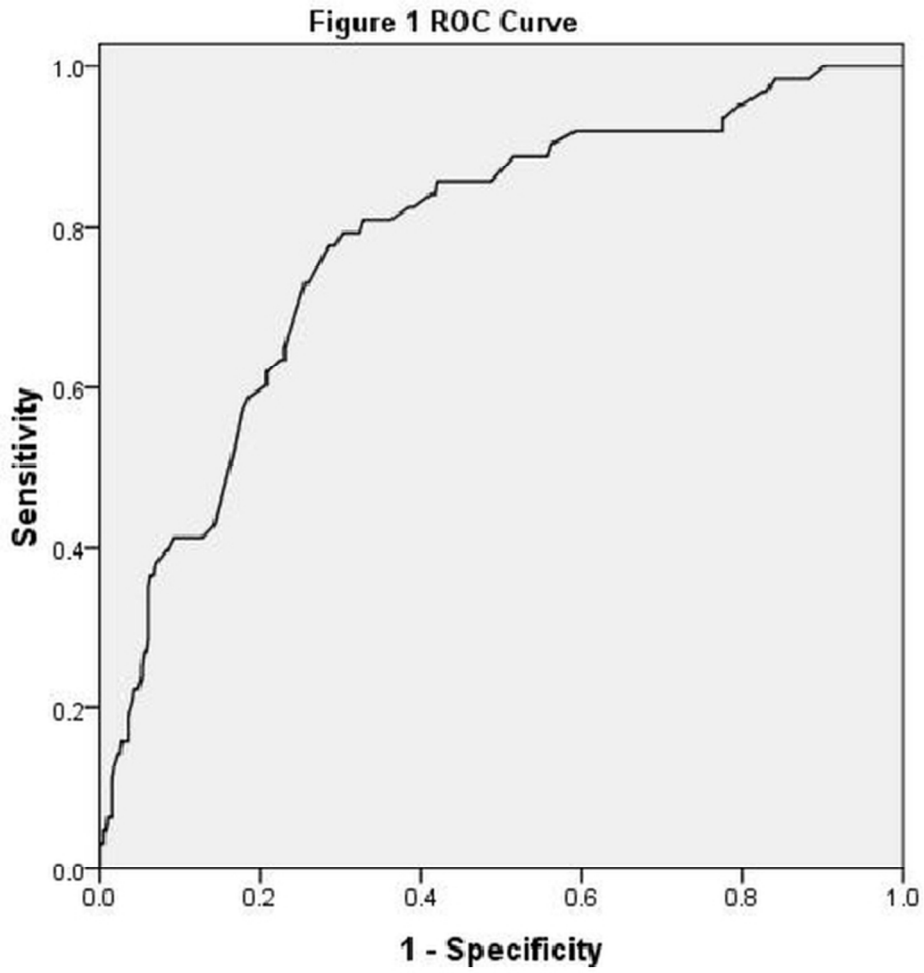
Table 2
Psychological Symptom of Distress 1 Month Post Genetic Testing Results
By Disease Type (N=475)

	Overall N (%)	Huntington	BRCA	Other Cancer
IES intrusion $\geq 17^a$	60 (13.0%)	5 (23.8%)	51 (12.5%)	4 (9.5%)
IES avoidance $\geq 17^a$	65 (13.7%)	5 (23.8%)	57 (14.0%)	3 (7.1%)
BSI-18 total $\geq 13^b$	95 (20.1%)	6 (28.6%)	86 (21.1%)	3 (7.1%)
<p>a. Shemesh E. et al (2004) Posttraumatic stress, non adherence, and adverse outcome in survivors of a myocardial infarction. <i>Psychosomatic Medicine</i>, 66: 521-526</p> <p>b. Zabora et al (2001): A new psychosocial screening instrument for use with cancer patients. <i>Psychosomatics</i>, 42:241-246</p>				

Table 3
GPRI Factor Solutions and Factor Loadings

	Factor Loadings	Communalities	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%				

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Diagonal segments are produced by ties.

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):

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| 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 |
| <u>If yes</u> , 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 |
| <u>If yes</u> , 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 <u>have</u> 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 <u>currently</u> 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

- | | | |
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| 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.

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

